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International application number: PCT/US2004/043474

International filing date: 22 December 2004 (22.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/533,024
Filing date: 29 December 2003 (29.12.2003)

Date of receipt at the International Bureau: 22 December 2004 (22.12.2004)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

1210333

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APPLICATION NUMBER: ***60/533,024***
FILING DATE: ***December 29, 2003***

Certified by

Jon W Dudas

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22855 U.S.PTO
122903

Docket No.: 59407US002

Transmittal of Provisional Application

Mail Stop Provisional Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

22387 U.S.PTO
60/533024
122903

Inventor(s): Tushar Kshirsagar, Woodbury, Minnesota and George W. Griesgraber, St. Paul, Minnesota

Title: PIPERAZINE, [1,4]DIAZEPANE, [1,4]DIAZOCANE, AND [1,5]DIAZOCANE FUSED IMIDAZOQUINOLINE AMINES

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1. ☒ Enclosed is the above-identified new provisional application for patent under 35 USC § 111(b)(1). It includes:
   96 Pages of Text
   0 Sheets of Drawings
2. ☐ Enclosed is an executed Assignment to 3M Innovative Properties Company and a completed Assignment Recordation Cover Sheet.
3. ☐ This invention was made under a contract with an agency of the U.S. Government:
   Agency: ______
   Contract No. ______
4. ☒ Correspondence Address: Robert W. Sprague
   Office of Intellectual Property Counsel
   3M Innovative Properties Company
   P.O. Box 33427
   St. Paul, Minnesota 55133-3427
5. ☒ Please charge the $160.00 filing fee under 37 CFR § 1.16(k) to Deposit Account No. 13-3723. One copy of this sheet marked duplicate is also enclosed.
6. ☒ Please charge to Deposit Account No. 13-3723 any fees under 37 CFR §§ 1.16 and 1.17, which may be required to file and during the entire pendency of this application. This authorization includes the fee for any necessary extension of time under 37 CFR § 1.136(a). To the extent any such extension should become necessary, it is hereby requested.
7. ☒ Enclosed is a return receipt postcard.

Respectfully submitted,

December 29, 2003
Date

By: [signature]
Robert W. Sprague, Reg. No.: 30,497
Telephone No.: (651) 733-4247

Office of Intellectual Property Counsel
3M Innovative Properties Company
Facsimile No.: (651) 736-3833

Filing of Papers and Fees by Express Mailing	
Pursuant to 37 CFR § 1.10, this application and the documents and fees listed on this transmittal letter are being deposited on the date indicated below with the United States Postal Service "Express Mail Post Office to Addressee" service addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450	
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PIPERAZINE, [1,4]DIAZEPANE, [1,4]DIAZOCANE, AND [1,5]DIAZOCANE FUSED IMIDAZOQUINOLINE AMINES

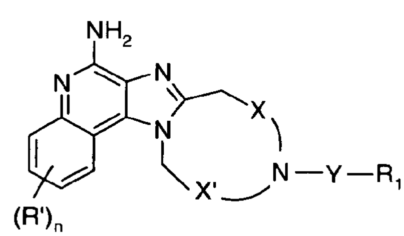
BACKGROUND

There has been a major effort in recent years to find compounds that modulate the immune system. Examples of such compounds, which have demonstrated cytokine inducing and immunomodulating activity, are disclosed by U.S. Patent Nos. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,352,784; 5,389,640; 5,446,153; 5,482,936; 5,494,916; 5,756,747; 6,110,929; 6,194,425; 6,331,539; 6,376,669; 6,451,810; 6,525,064; 6,545,016; 6,545,017; and 6,573,273; and PCT Publications WO 02/46188, WO 02/46189; WO 02/46190; WO 02/46191; WO 02/46192; and WO 02/46193.

Despite important progress in the effort to find immunomodulating compounds, there is still a critical scientific and medical need for additional compounds that have an ability to modulate aspects of the immune response, by induction or inhibition of cytokine biosynthesis or other mechanisms.

SUMMARY

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formulas I and II:



I

wherein:

X is a bond or straight chain or branched C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy wherein the hydroxy is bonded to a carbon atom other than a carbon atom adjacent a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the provision that when Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

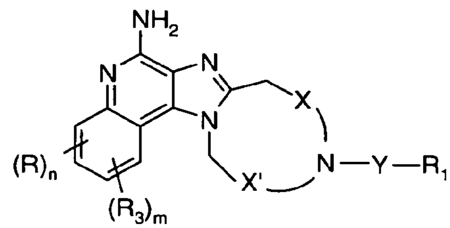
each R_6 is independently selected from the group consisting of =O and =S;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R' is a non-interfering substituent; and

n is 0 to 4;

or a pharmaceutically acceptable salt thereof.



II

wherein:

X is a bond or a straight chain or branched C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy wherein the hydroxy is bonded to a carbon atom other than a carbon atom adjacent a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case

of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the proviso that when Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X''-R_4$,

$-Z-X''-Y'-R_4$,

$-Z-X''-Y'-X''-Y'-R_4$, and

$-Z-X''-R_5$;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

n is 0 to 4;

each X" is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

each Y' is independently selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

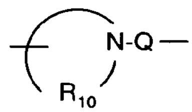
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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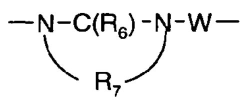

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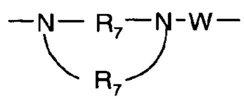

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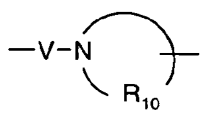

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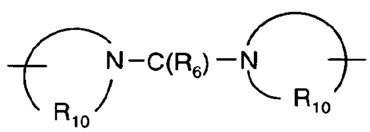

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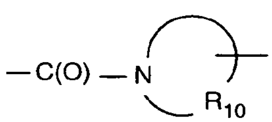
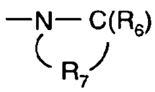
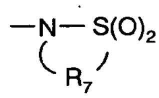
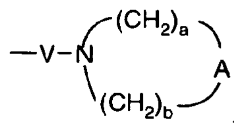
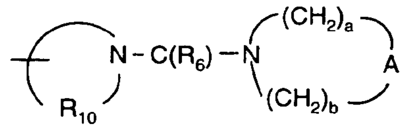


,

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

, , , and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)$;

each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

The compounds of Formulas I and II are useful as immune response modifiers (IRMs) due to their ability to induce cytokine biosynthesis (e.g., induce the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. This makes the compounds useful in the treatment of a variety of conditions, such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

In another aspect, the present invention provides pharmaceutical compositions containing the immune response modifier compounds, and methods of inducing cytokine biosynthesis in an animal, treating a viral disease in an animal, and treating a neoplastic disease in an animal, by administering an effective amount of one or more compounds of Formula I and/or Formula II and/or pharmaceutically acceptable salts thereof to the animal.

In another aspect, the invention provides methods of synthesizing compounds of Formulas I and II and intermediates useful in the synthesis of these compounds.

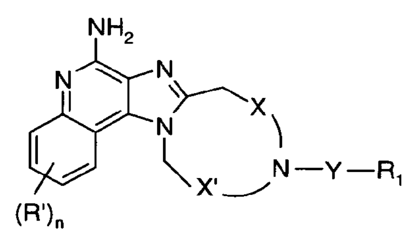
As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

In one aspect, the present invention provides compounds of the following Formula I:



I

wherein:

X is a bond or straight chain or branched C_{1-2} alkylene;

X' is straight chain or branched chain C_{1-8} alkylene optionally substituted with hydroxy wherein the hydroxy is bonded to a carbon atom other than a carbon atom adjacent a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the provision that when Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

each R_6 is independently selected from the group consisting of =O and =S;

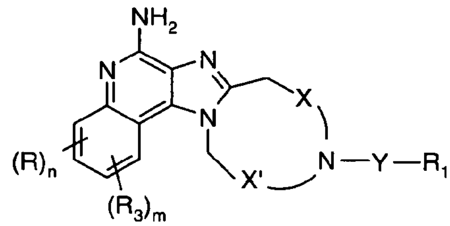
each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R' is a non-interfering substituent; and

n is 0 to 4;

or a pharmaceutically acceptable salt thereof.

The present invention also provides compounds of the following Formula II:



II

wherein:

X is a bond or straight chain or branched C_{1-2} alkylene;

X' is straight chain or branched chain C_{1-8} alkylene optionally substituted with hydroxy wherein the hydroxy is bonded to a carbon atom other than a carbon atom adjacent a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case

of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the proviso that when Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X''-R_4$,

$-Z-X''-Y'-R_4$,

$-Z-X''-Y'-X''-Y'-R_4$, and

$-Z-X''-R_5$;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

n is 0 to 4;

each X" is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

each Y' is independently selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

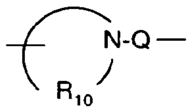
-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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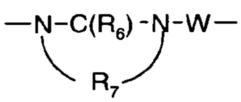

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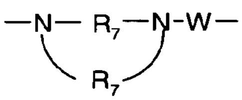

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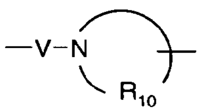

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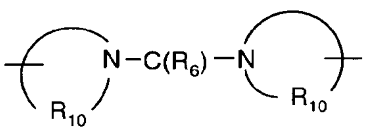

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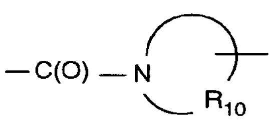

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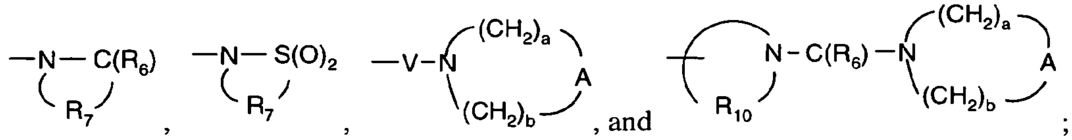
Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)$;

each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

Herein, "non-interfering" means that the ability of the compound or salt to modulate the biosynthesis of one or more cytokines is not destroyed by the non-interfering substituent. Illustrative non-interfering R' groups include those described above for R and R_3.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl,

cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. Likewise, "alkylenyl," "alkenylenyl," and "alkynylenyl" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

The term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl, and the like.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. Likewise, "arylenyl," "heteroarylenyl," and "heterocyclylenyl" are the divalent forms of the "aryl," "heteroaryl,"

and "heterocyclyl" groups defined above. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

In some embodiments of Formulas I and II, Y is $-S(O)_2-$ and R_1 is methyl.

In some embodiments of Formulas I or II, X is a bond and X' contributes one or two ring carbon atoms.

In some embodiments of Formulas I and II, n is 0.

In some embodiments of Formula II, m and n are 0.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

Preparation of the Compounds

Compounds of the invention can be prepared according to Reaction Scheme I, wherein R, R_1, X, X', Y, and n are as defined above, Hal is chloro, bromo, or iodo, and Boc is *tert*-butoxycarbonyl. Reaction Scheme I shows two routes to a 1*H*-imidazoquinolin-6-amine of Formula XVI; the routes are labeled Ia and Ib. In step (1) of Reaction Scheme I, a quinoline-3,4-diamine of Formula X is reacted with an acid halide of formula Hal-X-C(O)Cl or Hal-X-C(O)Br to provide a 1*H*-imidazoquinoline of Formula XI. The reaction is conveniently carried out by adding the acid halide to a solution of a quinoline-3,4-diamine of Formula X in a suitable solvent such as dichloromethane or 1,2-dichloroethane in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at an elevated temperature. The product can be isolated by conventional methods.

The reaction may afford an amide intermediate instead of the 1*H*-imidazoquinoline of Formula XI. The amide can be optionally isolated using conventional techniques and heated in a suitable solvent such as toluene to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XI. The cyclization can also be carried out in the presence of a base such as triethylamine.

Compounds of Formula X can be readily prepared using known synthetic routes; see for example, U.S. Patent Nos. 4,689,338 (Gerster), 5,268,376 (Gerster), 6,331,539 (Crooks et al.), 6,451,810 (Coleman et al.), 6,541,485 (Crooks et al.) and PCT Publication Nos.WO 02/46188, WO 02/46189, WO 02/46190, WO 02/46191, WO 02/46192, and WO 02/46188.

In step (2) of Reaction Scheme 1, a 1*H*-imidazoquinoline of Formula XI is cyclized by an intramolecular displacement of the halogen by the carbamate-protected amino group. The reaction is conveniently carried out by adding a base such as potassium *tert*-butoxide to a solution of a 1*H*-imidazoquinoline of Formula XI in a suitable solvent such as tetrahydrofuran. The reaction can be carried out at ambient temperature or at a sub-ambient temperature such as 0 °C. The product can be isolated using conventional methods.

In step (3a) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XII is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XIII using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XII in a solvent such as chloroform or dichloromethane. The reaction can be carried out at ambient temperature. The product can be isolated using conventional methods.

In step (4a) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XIII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XIV. Step (4) involves the activation of an *N*-oxide of Formula XIII by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding ammonium hydroxide to a solution of the *N*-oxide of Formula XIII in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature, and the product can be isolated from the reaction mixture using conventional methods.

In step (5a) of Reaction Scheme I, the Boc protecting group of a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XIV is removed under acidic conditions to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XV. The deprotection is conveniently carried out by adding a solution of hydrogen chloride in 1,4-dioxane or a solution of trifluoroacetic acid in dichloromethane to the 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XIV. The reaction may be run in a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature, and the product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (6a) of Reaction Scheme I, the secondary amine of the 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV or a salt thereof is converted to an amide, sulfonamide, sulfamide, or urea of Formula XVI using conventional methods. Formula XVI represents a subgenus of Formula II. In step (6a), a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV can react with an acid chloride of Formula $R_1C(O)Cl$ to provide a compound of Formula XVI in which Y is -C(O)-. In addition, a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV can react with sulfonyl chloride of Formula $R_1S(O)_2Cl$ or a sulfonic anhydride of Formula $(R_1S(O)_2)_2O$ to provide a compound of Formula XVI in which Y is $-S(O)_2-$. Numerous acid chlorides of Formula $R_1C(O)Cl$, sulfonyl chlorides of Formula $R_1S(O)_2Cl$, and sulfonic anhydrides of Formula $(R_1S(O)_2)_2O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction is conveniently carried out by adding the acid chloride of Formula $R_1C(O)Cl$, sulfonyl chloride of Formula $R_1S(O)_2Cl$, or sulfonic anhydride of Formula $(R_1S(O)_2)_2O$ to a solution of the amino-substituted 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV in a suitable solvent such as chloroform, dichloromethane, or *N,N*-dimethylformamide (DMF). Optionally a base such as triethylamine or *N,N*-diisopropylethylamine can be added. The reaction can be carried out at ambient temperature or a sub-ambient temperature such as 0 °C. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Ureas of Formula XVI, where Y is $-C(O)-N(R_8)-$ and R_8 is defined as above, can be prepared by reacting a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV or a salt thereof with isocyanates of Formula $R_1N{=}C{=}O$. Numerous isocyanates of Formula $R_1N{=}C{=}O$ are commercially available; others can be readily prepared using known synthetic methods.

The reaction can be conveniently carried out by adding the isocyanate of Formula $R_1N{=}C{=}O$ to a solution of the 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV in a suitable solvent such as DMF or chloroform. Optionally a base such as triethylamine or *N,N*-diisopropylethylamine can be added. The reaction can be carried out at ambient temperature or a sub-ambient temperature such as 0 °C. Alternatively, a compound of Formula XV can be treated with an isocyanate of Formula $R_1(CO)N{=}C{=}O$, a thioisocyanate of Formula $R_1N{=}C{=}S$, a sulfonyl isocyanate of Formula $R_1S(O)_2N{=}C{=}O$, or a carbamoyl chloride of Formula $R_1N\text{-}(R_8)\text{-}C(O)Cl$ to provide a compound of Formula XVI, where Y is $\text{-}C(O)\text{-}N(R_8)\text{-}(CO)\text{-}$, $\text{-}C(S)\text{-}N(R_8)\text{-}$, $\text{-}C(O)\text{-}N(R_8)\text{-}S(O)_2\text{-}$, or $\text{-}C(O)\text{-}N(R_8)\text{-}$, respectively. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Sulfamides of Formula XVI, where Y is $-S(O)_2\text{-}N(R_8)\text{-}$, can be prepared by reacting a compound or salt of Formula XV with sulfuryl chloride to generate a sulfamoyl chloride in situ, and then reacting the sulfamoyl chloride with an amine of formula $HN(R_8)R_1$. Alternatively, sulfamides of Formula XVI can be prepared by reacting a compound of Formula XV with a sulfamoyl chloride of formula $R_1(R_8)N\text{-}S(O)_2Cl$. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Many sulfonyl chlorides of Formula $R_1S(O)_2Cl$ and amines of Formula $HN(R_8)R_1$, and some sulfamoyl chlorides of formula $R_1(R_8)N\text{-}S(O)_2Cl$ are commercially available; others can be prepared using known synthetic methods.

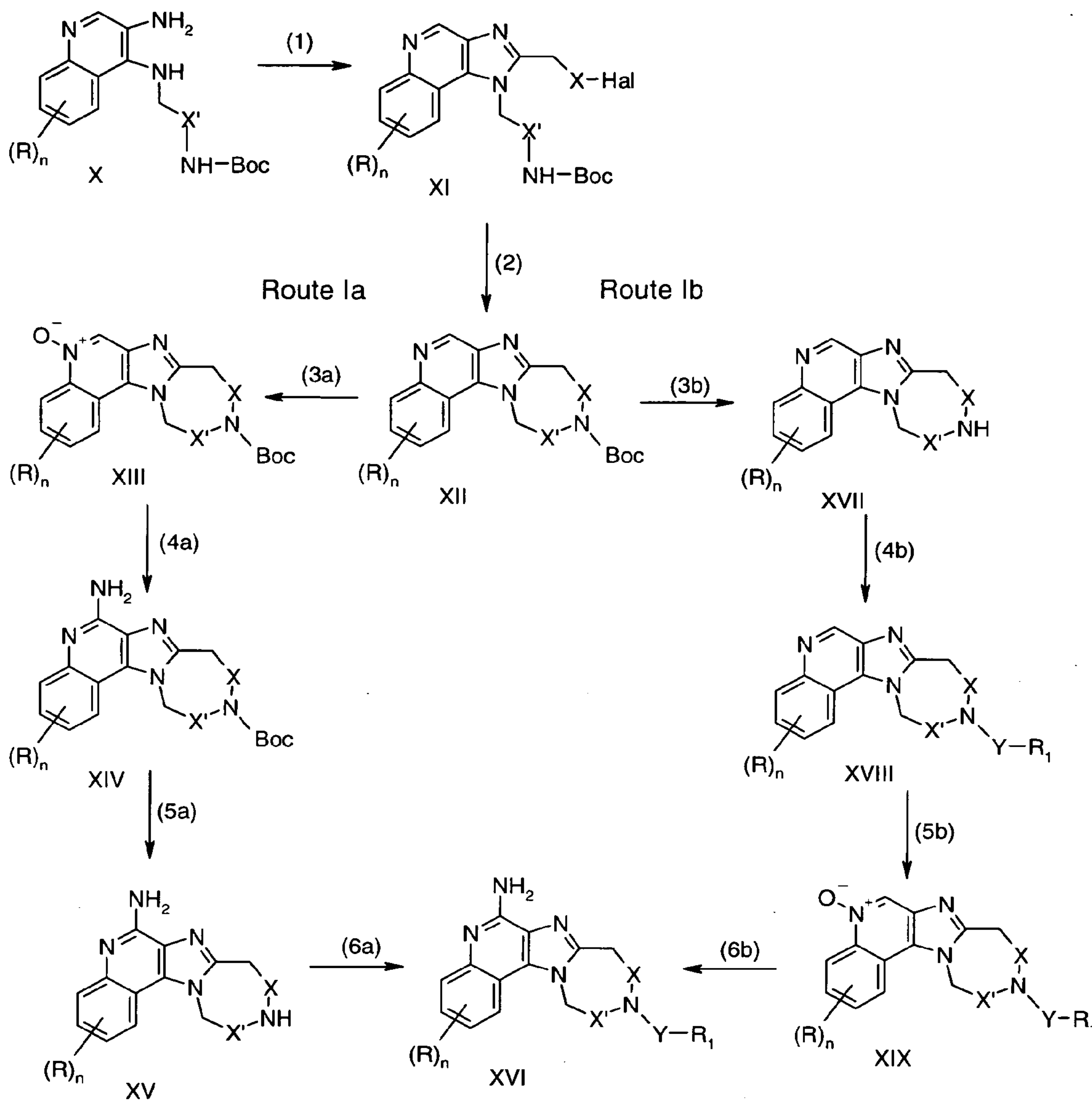
Compounds of Formula XVI where Y is a bond can be prepared by reductive alkylation of the secondary amine of the 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV. The alkylation is conveniently carried out in two parts by (i) adding an aldehyde or ketone to a solution of a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV or a salt thereof in a suitable solvent such as DMF in the presence of a base such as *N,N*-diisopropylethylamine. In part (ii) the reduction is carried out by adding a suitable reducing agent such as the borane-pyridine complex. Both part (i) and part (ii) can be carried out at ambient temperature, and the product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In steps (3b) and (4b) of Route Ib of Reaction Scheme I, the Boc protecting group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XII is first removed to product a 1*H*-

imidazo[4,5-*c*]quinoline of Formula XVII or a pharmaceutically acceptable salt thereof, which is then converted to an amide, sulfonamide, urea, or sulfamide of Formula XIII. Steps (3b) and (4b) of Route Ib can be carried out as described in steps (5a) and (6a) of Route Ia of Reaction Scheme I.

In steps (5b) and (6b) of Route Ib of Reaction Scheme I, a compound of Formula XVIII is first oxidized to a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XIX, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XVI. Steps (5b) and (6b) of Route Ib can be carried out as described in steps (3a) and (4a) of Route Ia of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme I



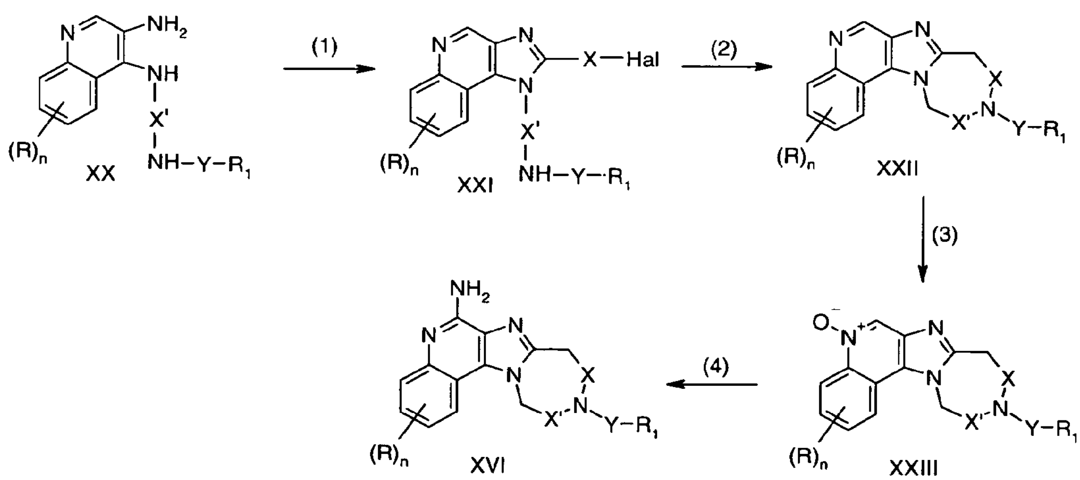
Compounds of the invention can also be prepared according to Reaction Scheme II, wherein R, R_1, X, X', Y, and n are as defined above and Hal is chloro, bromo, or iodo. In step (1) of Reaction Scheme II, a quinoline-3,4-diamine of Formula XX is reacted with an acid halide of formula Hal-X-C(O)Cl or Hal-X-C(O)Br to provide a 1*H*-imidazoquinoline of Formula XXI. The reaction is conveniently carried out as described for step (1a) of Reaction Scheme I.

Compounds of Formula XX can be readily prepared using known synthetic routes; see for example, U.S. Patent Nos. 4,689,338 (Gerster), 5,268,376 (Gerster), 6,331,539 (Crooks et al.), 6,451,810 (Coleman et al.), 6,541,485 (Crooks et al.) and PCT Publication Nos.WO 02/46188, WO 02/46189, WO 02/46190, WO 02/46191, WO 02/46192, and WO 02/46188.

In step (2) of Reaction Scheme II, a 1*H*-imidazoquinoline of Formula XXI is cyclized by an intramolecular displacement of the halogen by the carbamate-protected amino group. The reaction is conveniently carried out as described in step (2) of Reaction Scheme I to provide a compound of Formula XXII. Steps (1) and (2) may be effected in one step if the reaction in step (1) is heated at reflux for a day or two in a suitable solvent such as 1,2-dichloroethane.

In steps (3) and (4) of Reaction Scheme II, a compound of Formula XXII is first oxidized to a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXIII, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XVI. Steps (3) and (4) of Reaction Scheme II can be carried out as described in steps (3a) and (4a) of Route Ia of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme II



For some embodiments, compounds of the invention are prepared according to Reaction Scheme III, wherein R, R_1, X, X', Y, n, and Boc are as defined above; each Hal is

independently chloro, bromo, or iodo; R_{3a} is -Z-R_4, -Z-X"-R_4, -Z-X"-Y'-R_4, and -Z-X"-R_5; R_4, Y', and R_5 are as defined above; Z is a bond; and X" is alkylene or alkenylene. In step (1) of Reaction Scheme III, a quinoline-3,4-diamine of Formula XXIV is reacted with an acid halide of formula Hal-X-C(O)Cl or Hal-X-C(O)Br to provide a 1*H*-imidazoquinoline of Formula XXV. The reaction can be carried out as described in step (1) of Reaction Scheme I.

Compounds of Formula XXIV can be readily prepared using known synthetic routes; see for example, U.S. Patent Nos. 4,689,338 (Gerster), 5,268,376 (Gerster), 6,331,539 (Crooks et al.), 6,451,810 (Coleman et al.), 6,541,485 (Crooks et al.) and PCT Publication Nos.WO 02/46188, WO 02/46189, WO 02/46190, WO 02/46191, WO 02/46192, and WO 02/46188.

In step (2) of Reaction Scheme III, a 1*H*-imidazoquinoline of Formula XXV is cyclized by an intramolecular displacement of the halogen by the carbamate-protected amino group. The reaction can be carried out as described in step (2) of Reaction Scheme I to provide a compound of Formula XXVI.

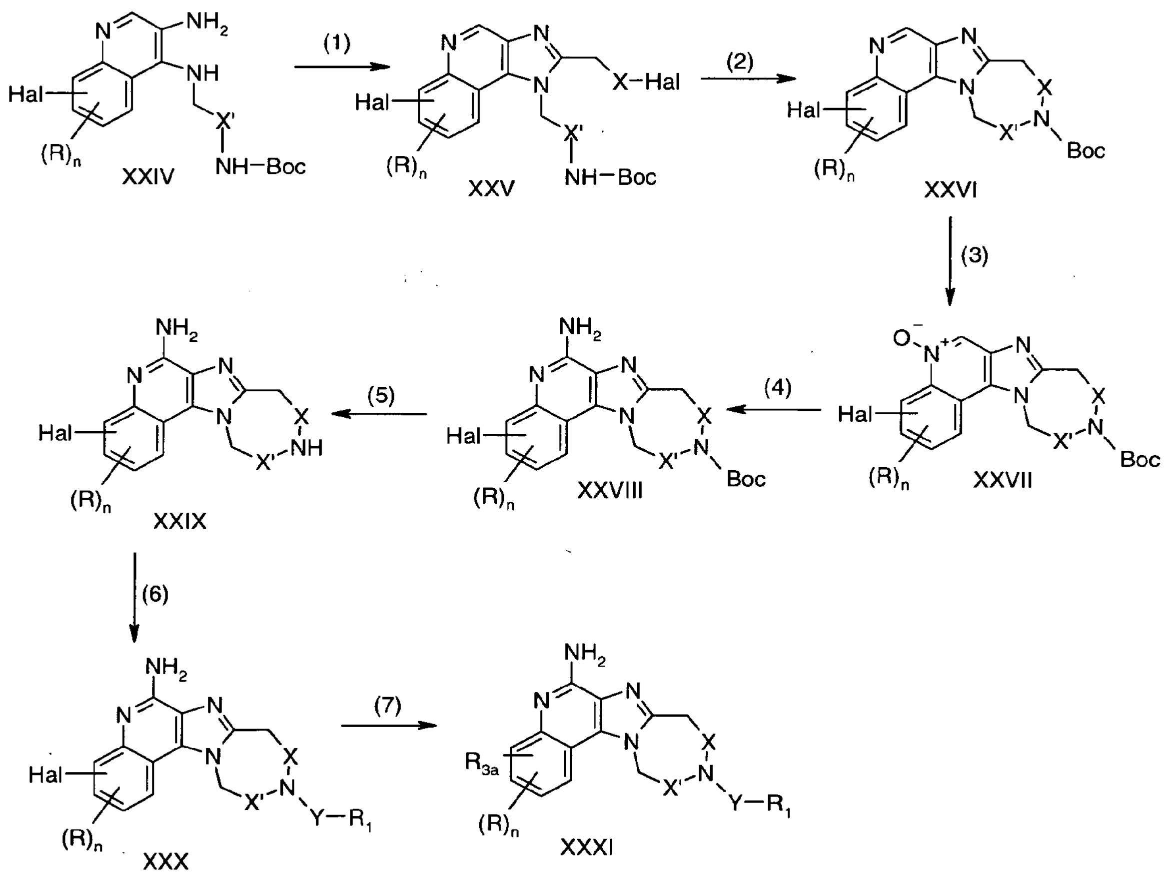
In steps (3) and (4) of Reaction Scheme III, a compound of Formula XXVI is first oxidized to a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXVII, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XXVIII. Steps (3) and (4) of Reaction Scheme III can be carried out as described in steps (3a) and (4a) of Route Ia of Reaction Scheme I.

In steps (5) and (6) of Reaction Scheme III, the Boc protecting group of a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XXVIII is first removed to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XXIX or a pharmaceutically acceptable salt thereof. The compound of Formula XXIX is then converted to an amide, sulfonamide, urea, or sulfamide of Formula XXX in step (6). Steps (5) and (6) of Reaction Scheme III can be carried out as described in steps (5a) and (6a) of Route Ia of Reaction Scheme I.

In step (7) of Reaction Scheme III, a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XXX is coupled with a boronic acid of Formula R_{3a}-B(OH)$_2$, an anhydride thereof, or a boronic acid ester of Formula R_{3a}-B(O-alkyl)$_2$ to provide an 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XXXI, which is a subgenus of Formula II. The Suzuki coupling is carried out by combining a compound of Formula XXX with a boronic acid or

an ester or anhydride thereof in the presence of palladium (II) acetate, triphenylphosphine, and a base such as sodium carbonate in a suitable solvent such as *n*-propanol. The reaction can be carried out at an elevated temperature (e.g., 80-100°C). Many boronic acids of Formula R_{3a}-$B(OH)_2$, anhydrides thereof, and boronic acid esters of Formula R_{3a}-B(O-alkyl)$_2$ are commercially available; others can be readily prepared using known synthetic methods. See, for example, Li, W. et al, *J. Org. Chem.*, *67*, 5394-5397 (2002). The product of Formula XXXI or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme III



Compounds of the invention can be prepared according to Reaction Scheme IV where R, R_1, X, X', Y, n, and Boc are as defined above; R_{3b} is -Z-R_4, -Z-X''-R_4,

-Z-X''-Y'-R_4,

-Z-X''-Y'-X''-Y'-R_4, or -Z-X''-R_5, where R_4, X'', Y', and R_5 are as defined above; and Z is -O-. In step (1) of Reaction Scheme IV, a benzyloxyaniline of Formula XXXII is treated with the condensation product generated from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and triethyl orthoformate to provide a dione of Formula XXXIII. The reaction is conveniently carried out by adding a solution of a benzyloxyaniline of Formula XXXII to a heated mixture of Meldrum's acid and triethyl orthoformate and heating the reaction at an elevated temperature such as 45 °C. The product can be isolated using conventional methods.

In step (2) of Reaction Scheme IV, a dione of Formula XXXIII undergoes thermolysis and cyclization to provide a benzyloxyquinolin-4-ol of Formula XXXIV. The reaction is conveniently carried out in a heat transfer fluid such as DOWTHERM A heat transfer fluid at a temperature between 200 and 250 °C. The product can be isolated using conventional methods.

In step (3) of Reaction Scheme IV, the benzyloxyquinolin-4-ol of Formula XXXIV is nitrated under conventional nitration conditions to provide a benzyloxy-3-nitroquinolin-4-ol of Formula XXXV. The reaction is conveniently carried out by adding nitric acid to the benzyloxyquinolin-4-ol of Formula XXXIV in a suitable solvent such as propionic acid and heating the mixture at an elevated temperature such as 125 °C. The product can be isolated using conventional methods.

In step (4) of Reaction Scheme IV, a benzyloxy-3-nitroquinolin-4-ol of Formula XXXV is chlorinated using conventional chlorination chemistry to provide a benzyloxy-4-chloro-3-nitroquinoline of Formula XXXVI. The reaction is conveniently carried out by treating the benzyloxy-3-nitroquinolin-4-ol of Formula XXXV with phosphorous oxychloride in a suitable solvent such as DMF. The reaction can be carried out at an elevated temperature such as 100 °C, and the product can be isolated using conventional methods.

In step (5) of Reaction Scheme IV, a benzyloxy-4-chloro-3-nitroquinoline of Formula XXXVI is treated with an amine of Formula Boc-NH-X'-CH_2-NH_2 to provide a benzyloxy-3-nitroquinolin-4-amine of Formula XXXVII. Several amines of Formula

Boc-NH-X'-CH_2-NH_2 are commercially available; others can be prepared by known synthetic methods. The reaction is conveniently carried out by adding the amine of Formula Boc-NH-X'-CH_2-NH_2 to a solution of the benzyloxy-4-chloro-3-nitroquinoline of Formula XXXVI in a suitable solvent such as dichloromethane or methanol in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at an elevated temperature such as, for example, the reflux temperature of the solvent. The reaction product can be isolated using conventional methods.

In step (6) of Reaction Scheme IV, a benzyloxy-3-nitroquinolin-4-amine of Formula XXXVI is reduced to provide a benzyloxyquinoline-3,4-diamine of Formula XXXVIII. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent such as toluene, methanol, or acetonitrile. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

Alternatively, the reduction in step (6) can be carried out using nickel boride, prepared *in situ* from sodium borohydride and nickel(II) chloride. The reduction is conveniently carried out by adding a solution of the benzyloxy-3-nitroquinolin-4-amine of Formula XXXVII in a suitable solvent or solvent mixture such as dichloromethane/methanol to a mixture of excess sodium borohydride and catalytic nickel(II) chloride in methanol. The reaction can be carried out at ambient temperature. The product can be isolated using conventional methods.

In step (7) of Reaction Scheme IV, a benzyloxyquinoline-3,4-diamine of Formula XXXVIII is treated with an acid halide of formula Hal-X-C(O)Cl or Hal-X-C(O)Br to provide a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline of Formula XXXIX. The reaction can be carried out as described in step (1) of Reaction Scheme I.

In step (8) of Reaction Scheme IV, a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline of Formula XXXIX is cyclized by an intramolecular displacement of the halogen by the carbamate-protected amino group. The reaction can be carried out as described in step (2) of Reaction Scheme I to provide a compound of Formula XL.

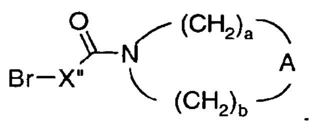
In steps (9) and (10) of Reaction Scheme IV, the Boc protecting group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XL is first removed to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XLI or a pharmaceutically acceptable salt thereof. The compound of Formula XLI is then converted to an amide, sulfonamide, urea, or sulfamide of Formula XLII in step (10). Steps (9) and (10) of Reaction Scheme IV can be carried out as described in steps (5a) and (6a) of Route Ia of Reaction Scheme I.

In step (11) of Reaction Scheme IV, the benzyl group of a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline of Formula XLII is cleaved to provide a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII. The cleavage is conveniently carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst such as palladium on carbon in a solvent such as ethanol. Alternatively, the reaction can be carried out by transfer hydrogenation in the presence of a suitable hydrogenation catalyst. The transfer hydrogenation is conveniently carried out by adding ammonium formate to a solution of a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline of Formula XLII in a suitable solvent such as ethanol in the presence of a catalyst such as palladium on carbon. The reaction is carried out at an elevated temperature, for example, the reflux temperature of the solvent. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (12) of Reaction Scheme IV a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII is converted to an ether-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XLIV using a Williamson-type ether synthesis. The reaction is effected by treating a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII with an alkyl halide of Formula Halide-R_4, Halide-X"-Y'-R_4, or Halide-X"-R_5 in the presence of a base. The reaction is conveniently carried out by combining a reagent of Formula Halide-R_4, Halide-X"-Y'-R_4, or Halide-X"-R_5 with a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII in a solvent such as DMF in the presence of a suitable base such as cesium carbonate. The reaction can be carried out at ambient temperature or at an elevated temperature, for example 65 °C or 85 °C. Alternatively, the reaction can be carried out by treating a solution of a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII in a solvent such as DMF with sodium hydride and then adding a reagent of Formula Halide-R_4, Halide-X"-Y'-R_4, or Halide-X"-R_5. The

product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Numerous reagents of Formulas Halide-R_4 and Halide-X"-Y'-R_4 are commercially available, for example, bromo-substituted ketones, esters, and heterocycles. Other reagents of Formulae Halide-R_4, Halide-X"-Y'-R_4, or Halide-X"-R_5 can be prepared using conventional synthetic methods; for example, a bromo-substituted acid halide of Formula ClC(O)-X"-Br can be treated with a secondary amine in a suitable solvent such as dichloromethane to provide a variety of bromo-substituted amides of Formula Br-X"-C(O)-N(R_8)-R_4 or

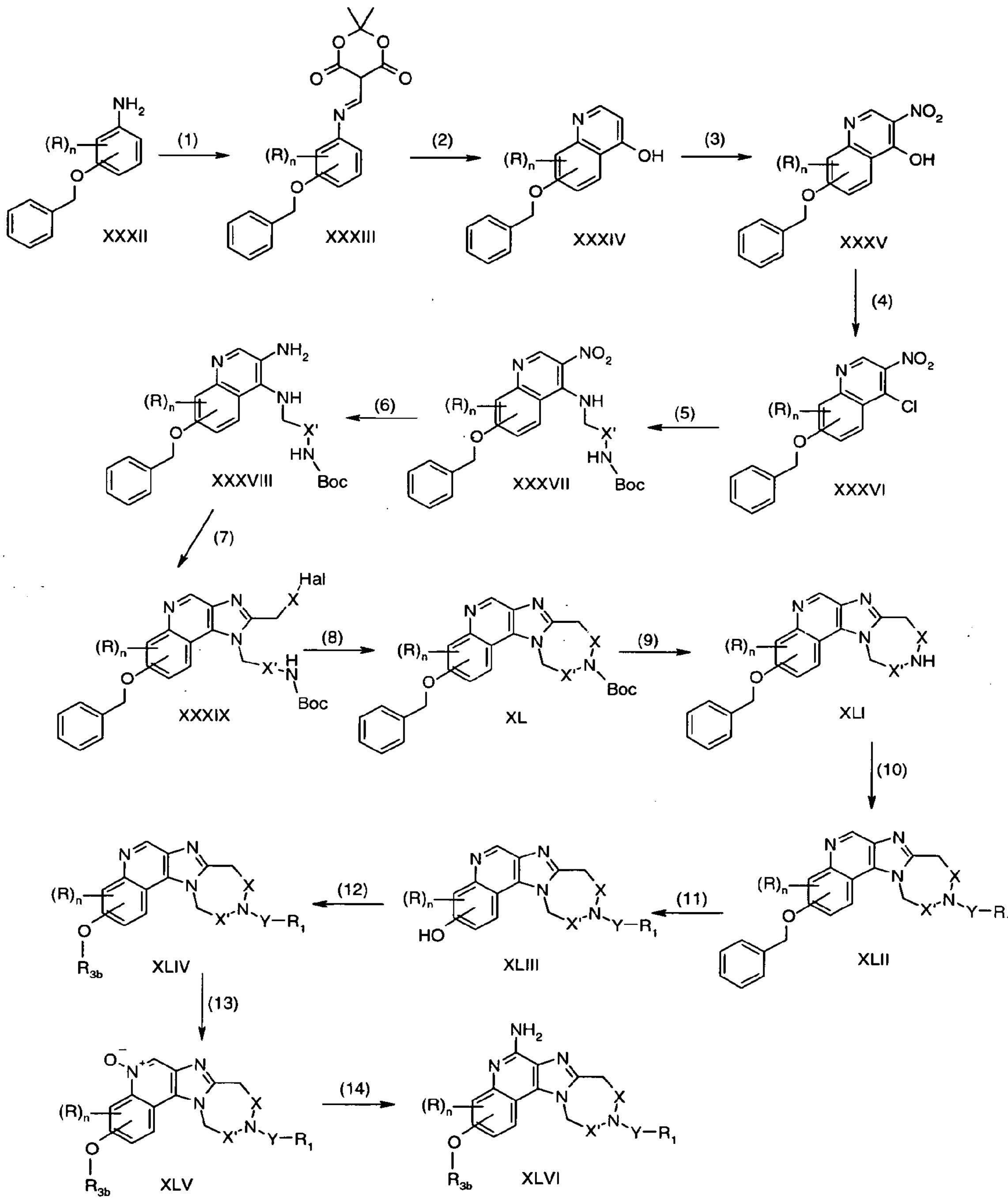


The reaction can be run at a sub-ambient temperature such as -25 °C, and the product can be isolated using conventional methods.

Step (12) of Reaction Scheme IV can alternatively be carried out by treating a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII with an alcohol of Formula HO-X"-Y'-R_4, HO-X"-R_5, or HO-R_4 under Mitsunobu reaction conditions. Numerous alcohols of these formulas are commercially available, and others can be prepared using conventional synthetic methods. The reaction is conveniently carried out by out by adding triphenylphosphine and an alcohol of Formula HO-X"-Y'-R_4, HO-X"-R_5, or HO-R_4 to a solution of a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII in a suitable solvent such as tetrahydrofuran and then slowly adding diisopropyl azodicarboxylate or diethyl azodicarboxylate. The reaction can be carried out at ambient temperature or at a sub-ambient temperature, such as 0 °C. The product can be isolated using conventional methods.

In steps (13) and (14) of Reaction Scheme IV, an ether-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XLIV is first oxidized to a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XLV, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XLVI, a subgenus of Formula II. Steps (13) and (14) of Reaction Scheme IV can be carried out as described in steps (3a) and (4a) of Route Ia of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme IV



R_{3a}

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound of the invention as described above in combination with a pharmaceutically acceptable carrier.

The term "a therapeutically effective amount" or "effective amount" means an amount of the compound sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg, of the compound to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

The compounds of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds according to the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and

IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. The animal to which the compound or composition is administered for induction of cytokine biosynthesis may have a disease as described infra, for example a viral disease or a neoplastic disease, and administration of the compound may provide therapeutic treatment. Alternatively, the compound may be administered to the animal prior to the animal acquiring the disease so that administration of the compound may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, the compounds of the invention affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds may cause proliferation and differentiation of B-lymphocytes.

Compounds of the invention also have an effect on the acquired immune response. For example, the production of the T helper type 1 (Th1) cytokine IFN-γ is induced indirectly and the production of the T helper type 2 (Th2) cytokines IL-4, IL-5 and IL-13 are inhibited upon administration of the compounds.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which IRMs identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, genital warts, common warts, plantar warts, hepatitis B, hepatitis C, molluscum contagiosum, and diseases resulting from infection by Variola, Herpes simplex virus (Type I and/or Type II), HIV, CMV, VZV, Rhinovirus, Adenovirus, Coronavirus, Influenza, or Para-influenza;

(b) bacterial diseases including, but not limited to, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococci, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such as fungal diseases, leishmaniasis, chlamydia, candidiasis, aspergillosis, cryptococcal meningitis, pneumocystis carnii pneomonia, cryptosporidiosis, histoplasmosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, hairy cell leukemia, Karposi's sarcoma, melanoma, renal cell carcinoma, myelogeous leukemia, multiple myeloma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, cutaneous T-cell lymphoma, B-cell lymphoma, and other cancers; and

(e) TH-2 mediated, atopic, and autoimmune diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, systemic lupus erythematosis, essential thrombocythaemia, multiple sclerosis, Ommen's syndrome, discoid lupus, alopecia areata, inhibition of keloid formation and other types of scarring, and enhancing would healing, including chronic wounds.

IRMs identified herein also may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such live viral and bacterial immunogens and inactivated viral, tumor-derived, protozoal, organism-derived, fungal, and bacterial immunogens, toxoids, toxins, polysaccharides, proteins, glycoproteins, peptides, cellular vaccines, DNA vaccines, recombinant proteins, glycoproteins, and peptides, and the like, for use in connection with, e.g., BCG, cholera, plague, typhoid, hepatitis A, B, and C, influenza A and B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria,

hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, and yellow fever.

IRMs may also be particularly helpful in individuals having compromised immune function. For example, IRM compounds may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of formula (I) to the animal.

An amount of a compound effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased over the background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

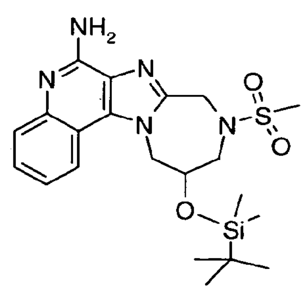
Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

In the examples below, some of the compounds were purified by preparative high performance liquid chromatography (HPLC) using a Waters Fraction Lynx automated purification system. The prep HPLC fractions were analyzed using a Micromass LC/TOF-MS, and the appropriate fractions were combined and centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. In order to maximize purity, some of the compounds were sent through the purification process twice. A variety of chromatographic conditions were used for separations. Column: Phenomenex Luna C18(2), 21.2 x 50 millimeters (mm), 10 micron particle size; or Waters XTerra C18, 19 x 50 millimeters (mm), 5 micron particle size; non-linear gradient elution from 5 to 95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile; fraction collection by mass-selective triggering.

Example 1

11-(*tert*-Butyldimethylsilanyloxy)-9-methanesulfonyl-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

Under a nitrogen atmosphere, a solution of di-*tert*-butyl dicarbonate (145.35 g, 665.98 mmol) in 1,4-dioxane (400 mL) was added dropwise with stirring to a solution of 2-hydroxy-1,3-diaminopropane (300.00 g, 332.85 mmol) in methanol (500 mL) over a

period of six hours. The reaction was stirred overnight at ambient temperature and then concentrated under reduced pressure. The residue was dissolved in 10% citric acid in water, and additional citric acid was added to adjust the solution to pH 4. The resulting solution (1-1.5 L) was washed with dichloromethane (3 x 500 mL) and then adjusted to pH 12 with the addition of 50% aqueous sodium hydroxide. The basic solution was extracted with chloroform (7 x 500 mL), and the combined extracts were concentrated under reduced pressure and dried overnight under high vacuum to provide 108.19 g of *tert*-butyl (3-amino-2-hydroxypropyl)carbamate as a white solid.

Part B

Under a nitrogen atmosphere, triethylamine (72 g, 710 mmol) was added to a solution of 4-chloro-3-nitroquinoline (98.9 g, 474 mmol) in *N,N*-dimethylformamide (DMF) (1 L). A solution of *tert*-butyl (3-amino-2-hydroxypropyl)carbamate (108.19 g, 569 mmol) in dioxane (800 mL) was slowly added, and the reaction was stirred overnight at ambient temperature and then poured into water (3 L) with continuous stirring. A precipitate formed and was isolated by filtration, washed with water, and dried for three days in a vacuum oven at 65 °C to provide 167.54 g of *tert*-butyl [2-hydroxy-3-(3-nitroquinolin-4-ylamino)propyl]carbamate as a bright yellow powder.

Part C

Triethylamine (111.7 g, 1.104 mol) was added to a solution of *tert*-butyl [2-hydroxy-3-(3-nitroquinolin-4-ylamino)propyl]carbamate (100.0 g, 275.95 mmol) in DMF (400 mL). A solution of *tert*-butyldimethylsilyl chloride (TBDMSCl) (91.5 g, 607 mmol) in DMF (140 mL) was slowly added, and the reaction was stirred overnight at ambient temperature. An analysis by high-performance liquid chromatography (HPLC) indicated the presence of starting material, and additional triethylamine (1 equivalent) and TBDMSCl (0.5 equivalent) were added. The reaction was stirred overnight at ambient temperature, and a large excess of TBDMSCl was added. The product mixture was filtered to remove a solid, and the filtrate was concentrated under reduced pressure. The residue was dissolved in chloroform, and the resulting solution was washed with aqueous ammonium chloride (3 x), aqueous sodium bicarbonate (2 x), and brine and then

concentrated under reduced pressure. The resulting solid was dried overnight under high vacuum. The crude solid was recrystallized from acetonitrile, and two crops of crystals were collected to provide 110.18 g of *tert*-butyl [2-(*tert*-butyldimethylsilanyloxy)-3-(3-nitroquinolin-4-ylamino)propyl]carbamate as a white powder.

Part D

A solution of *tert*-butyl [2-(*tert*-butyldimethylsilanyloxy)-3-(3-nitroquinolin-4-ylamino)propyl]carbamate (110.18 g, 231.16 mmol) in dichloromethane (500 mL) was added to a Parr vessel. The system was purged with nitrogen, and 10% palladium on carbon (14.76 g, 138.7 mmol) was added. The vessel was placed under hydrogen pressure (30 psi, 2.1 x 10^5 Pa) and shaken for four hours. The reaction mixture was filtered, and the filtrate was passed through a plug of silica gel and concentrated under reduced pressure to provide 103.45 g of *tert*-butyl [3-(3-aminoquinolin-4-ylamino)-2-(*tert*-butyldimethylsilanyloxy)propyl]carbamate.

Part E

Triethylamine (46.2 g, 456 mmol) was added to a solution of *tert*-butyl [3-(3-aminoquinolin-4-ylamino)-2-(*tert*-butyldimethylsilanyloxy)propyl]carbamate (101.9 g, 228.1 mmol) in 1,2-dichloroethane (600 mL). A solution of chloroacetyl chloride (28.3 g, 251 mmol) in 1,2-dichloroethane was added dropwise, and the reaction was stirred overnight at ambient temperature. The reaction mixture was filtered to remove a solid, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting sequentially with 95.5:0.5 and 95:5 dichloromethane:methanol), and the purified product was dried overnight under high vacuum to provide 71.93 g of *tert*-butyl [2-(*tert*-butyldimethylsilanyloxy)-3-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate.

Part F

Potassium *tert*-butoxide (116.1 mL of a 1M solution in tetrahydrofuran) was added to a solution of *tert*-butyl [2-(*tert*-butyldimethylsilanyloxy)-3-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (42.72 g, 84.57 mmol) in anhydrous

tetrahydrofuran (THF) (50 mL), and the reaction was stirred overnight at ambient temperature and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 99:1 to 95:5) to provide 20.23 g of *tert*-butyl [11-(*tert*-butyldimethylsilanyloxy)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl]carbamate.

Part G

Trifluoroacetic acid (500 mL of a 10% solution in dichloromethane) was added to *tert*-butyl [11-(*tert*-butyldimethylsilanyloxy)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl]carbamate (9.23 g, 19.7 mmol), and the reaction was stirred at ambient temperature for 75 minutes. The solvent was removed under reduced pressure, and the residue was shaken with triethylamine (300 mL) and dichloromethane. The solution was concentrated under reduced pressure, and the product was dried under high vacuum for two hours and used in the next step without removing the triethylamine trifluoroacetate salt.

Part H

Triethylamine (7.97 g, 78.8 mmol) was added to a solution of the material from Part G in dichloromethane (500 mL). Methanesulfonyl chloride (2.71 g, 23.6 mmol) was slowly added. The reaction was stirred at ambient temperature for one hour, washed with brine and sodium bicarbonate, and concentrated under reduced pressure. The residue was dried for two days under high vacuum to provide 8.78 g of 11-(*tert*-butyldimethylsilanyloxy)-9-methanesulfonyl-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinoline. The product was combined with material made in a separate run.

Part I

3-Chloroperoxybenzoic acid (9.92 g of 77% pure material, 57.47 mmol) (mCPBA) was added to a solution of 11-(*tert*-butyldimethylsilanyloxy)-9-methanesulfonyl-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinoline (16.47 g, 36.88

mmol) in chloroform (200 mL), and the reaction was stirred overnight at ambient temperature. Additional mCPBA (1-1.5 equivalents) was added, and the reaction was stirred for two hours, washed with brine and sodium bicarbonate, and concentrated under reduced pressure.

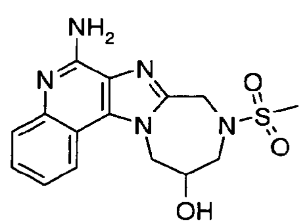
Part J

Ammonium hydroxide (150 mL) was added with vigorous stirring to a solution of the material from Part I in chloroform (200 mL). *p*-Toluenesulfonyl chloride (7.73 g, 40.6 mmol) was added in portions, and the reaction was stirred overnight and then concentrated under reduced pressure. The residue was dissolved in chloroform and poured into ethyl acetate (800 mL) to form a precipitate, which was isolated by filtration and washed with methanol. The filtrate was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (50 mL) and refrigerated overnight. Crystals formed and were isolated by filtration, and two additional crops of crystals were obtained in the same manner. The crystals were combined and dried in a vacuum oven to provide 6.69 g of 11-(*tert*-butyldimethylsilanyloxy)-9-methanesulfonyl-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as a white powder, mp 256-258 °C.

Anal. Calcd for $C_{21}H_{31}N_5O_3SSi$: C, 54.63; H, 6.77; N, 15.17. Found: C, 54.63; H, 6.90; N, 14.91.

Example 2

6-Amino-9-methanesulfonyl-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-ol



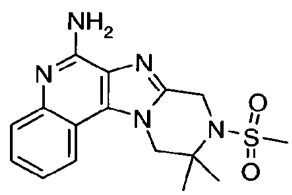
A suspension of 11-(*tert*-butyldimethylsilanyloxy)-9-methanesulfonyl-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (1.0 g, 2.2 mmol) in anhydrous THF (30 mL) was cooled to -20 °C, and tetrabutylammonium fluoride (2.383

mL of a 1 M solution in THF) was slowly added. The reaction was stirred overnight, and a precipitate formed. The cold reaction mixture was filtered, and the isolated precipitate was washed with THF and dried under high vacuum to provide 313.7 mg of 6-amino-9-methanesulfonyl-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-ol as a white solid, mp 282 °C.

Anal. Calcd for $C_{15}H_{17}N_5O_3S$: C, 50.81; H, 5.06; N, 19.75. Found: C, 51.02; H, 5.21; N, 19.58.

Example 3

10,10-Dimethyl-9-methanesulfonyl-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

Under a nitrogen atmosphere, a solution of triethylamine (167 mL, 1.20 mol) in anhydrous dichloromethane (1 L) was cooled to 0 °C. Solid 4-chloro-3-nitroquinoline (121.6 g, 585 mmol) was added over a period of five minutes, and the reaction was allowed to warm to ambient temperature slowly and stirred for two days. The solvent was removed under reduced pressure, and the resulting yellow solid was shaken with water (1 L) for several minutes and then isolated by filtration, washed with water (3 x 200 mL), and dried under vacuum for four days to provide 149 g of 2-methyl-N^1-(3-nitroquinolin-4-yl)propane-1,2-diamine as a bright yellow powder.

Anal. Calcd for $C_{13}H_{16}N_4O_2$: C, 59.53; H, 6.23; N, 21.36. Found: C, 59.23; H, 6.22; N, 21.45.

The product was dissolved in isopropanol (2 x 100 mL), concentrated under reduced pressure, dissolved in chloroform (2 x 100 mL), concentrated under reduced pressure, and finally dried under vacuum overnight.

Part B

Under a nitrogen atmosphere, a suspension of 2-methyl-N^1-(3-nitroquinolin-4-yl)propane-1,2-diamine (93 g, 358 mmol) and triethylamine (100 mL, 717 mmol) in anhydrous dichloromethane (1 L) was cooled to 0 °C. Methanesulfonyl chloride (27.7 mL, 358 mmol) was added over a period of 20 minutes. The reaction was allowed to warm to ambient temperature and stirred overnight. Additional methanesulfonyl chloride (9.2 mL) was added over a period of five minutes, and the reaction was stirred for an additional day. Additional methanesulfonyl chloride (2.0 mL) was added, and the reaction was stirred for two hours. The solvent was removed under reduced pressure, and the residue was triturated with water (800 mL) at 50 °C, isolated by filtration, and washed with water to provide 116 g of *N*-[1,1-dimethyl-2-(3-nitroquinolin-4-ylamino)ethyl]methanesulfonamide as a yellow powder.

Part C

A solution of *N*-[1,1-dimethyl-2-(3-nitroquinolin-4-ylamino)ethyl]methanesulfonamide (4.0 g, 12 mmol) in acetonitrile (200 mL) was added to a Parr vessel charged with 5% platinum on carbon (0.5 g) and purged with nitrogen. The vessel was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) and shaken overnight. The reaction was filtered through a layer of CELITE filter aid, and the filter cake was washed with acetonitrile and dichloromethane until the filtrate was colorless. The filtrate was concentrated under reduced pressure to provide 3.51 g of *N*-[2-(3-aminoquinolin-4-ylamino)-1,1-dimethylethyl]methanesulfonamide as a yellow powder.

Part D

Under a nitrogen atmosphere, a solution of *N*-[2-(3-aminoquinolin-4-ylamino)-1,1-dimethylethyl]methanesulfonamide (2.65 g, 8.59 mmol) in 1,2-dichloroethane (100 mL) was cooled to 0 °C. Triethylamine (2.4 mL, 17 mmol) and chloroacetyl chloride (0.82 mL, 10.3 mmol) were sequentially added, and the reaction was allowed to warm to ambient temperature, stirred overnight, then heated at reflux for 1.5 days. The reaction was washed with saturated aqueous sodium bicarbonate (2 x 100 mL) and brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 1.92 g of

10,10-dimethyl-9-methanesulfonyl-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinoline as a brown solid, which was used without purification.

Part E

In one portion mCPBA (0.87 g of 60% purity, 3.0 mmol) was added to a solution of 10,10-dimethyl-9-methanesulfonyl-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinoline (0.98 g, 3.0 mmol) in chloroform (50 mL), and the reaction was stirred for three hours at ambient temperature under a nitrogen atmosphere. The reaction mixture was washed with 1% aqueous sodium carbonate (50 mL), and the aqueous solution was extracted with chloroform (3 x 50 mL). The combined organic fractions were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 0.91 g of 10,10-dimethyl-9-methanesulfonyl-5-oxido-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinoline as an orange solid.

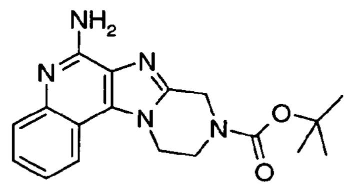
Part F

Ammonium hydroxide (5 mL) was added with vigorous stirring to a suspension of 10,10-dimethyl-9-methanesulfonyl-5-oxido-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinoline (0.91 g, 2.6 mmol) in dichloromethane (25 mL). *p*-Toluenesulfonyl chloride (0.50 g, 2.6 mmol) was added in one portion, and the reaction was stirred for four hours at ambient temperature. The organic layer was separated and washed with 1% aqueous sodium carbonate (50 mL) and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting orange solid (0.77 g) was recrystallized from 1,2-dichloroethane to provide 10,10-dimethyl-9-methanesulfonyl-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as a white powder, mp 227-228 °C.

Anal. Calcd for $C_{16}H_{19}N_5O_2S$: C, 55.64; H, 5.54; N, 20.27. Found: C, 55.35; H, 5.61; N, 20.07.

Example 4

tert-Butyl (6-amino-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-9-yl)carbamate



Part A

Triethylamine (58.2 g, 575 mmol) and 4-chloro-3-nitroquinoline (80.0 g, 384 mmol) were added to a solution of *tert*-butyl *N*-(2-aminoethyl)carbamate (67.6 g, 422 mmol) in DMF (300 mL), and the reaction was stirred overnight at ambient temperature. Water (600 mL) was added, and the resulting mixture was stirred for one hour. A precipitate formed and was isolated by filtration, washed with water (3 x 150 mL), and dried for two days in a vacuum oven at 45 °C to provide 125.36 g of *tert*-butyl [2-(3-nitroquinolin-4-ylamino)ethyl]carbamate as a yellow solid.

Part B

A solution of *tert*-butyl [2-(3-nitroquinolin-4-ylamino)ethyl]carbamate (20.0 g, 60.2 mmol) in a 2:1 mixture of dichloromethane:methanol (500 mL) was added to a Parr vessel. The system was purged with nitrogen, and 5% platinum on carbon (7.04 g, 36.1 mmol) was added. The vessel was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) and shaken overnight. The reaction mixture was filtered and concentrated under reduced pressure to provide 15.65 g of *tert*-butyl [2-(3-aminoquinolin-4-ylamino)ethyl]carbamate.

Part C

A modification of the method described in Part E of Example 1 was used to treat *tert*-butyl [2-(3-aminoquinolin-4-ylamino)ethyl]carbamate (15.65 g, 51.76 mmol) with triethylamine (10.82 mL, 77.64 mmol) followed by chloroacetyl chloride (4.5 mL, 57 mmol). The reaction was carried out in dichloromethane (60 mL). After the reaction mixture was filtered, the filtrate was washed with dilute aqueous sodium bicarbonate,

dried over magnesium sulfate, and concentrated under reduced pressure to provide *tert*-butyl [2-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate as an amber-colored solid, which was combined with material from two other runs for use in the next step.

Part D

Under a nitrogen atmosphere, a solution of *tert*-butyl [2-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (54.94 g, 152.3 mmol) in THF (400 mL) was cooled to 0 °C; a solution of potassium *tert*-butoxide (18.79 g of a 1 M solution in THF, 167.5 mmol) was added slowly. The reaction was stirred at 0 °C for three hours and then at ambient temperature overnight. The THF was removed under reduced pressure, and a 1:1 mixture of water and saturated aqueous sodium bicarbonate was added. The aqueous mixture was extracted with dichloromethane, and the combined extracts were washed sequentially with water and brine and concentrated under reduced pressure to provide 29.54 g of *tert*-butyl (8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl)carbamate.

Part E

mCPBA (26.1 g of 77% pure material, 118 mmol) was added in small portions to a solution of *tert*-butyl (8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl)carbamate (29.54 g, 91.06 mmol) in chloroform (500 mL), and the reaction was stirred for one hour at ambient temperature. Aqueous sodium carbonate (400 mL of a 1% solution) was added, and the mixture was stirred for 30 minutes. The organic layer was separated, washed with 1% aqueous sodium carbonate (2 x 300 mL). Citric acid (10% aqueous solution) was added to aid in the separation. The organic layer was then washed twice with 10% aqueous citric acid, and the combined aqueous washings were extracted with chloroform (3 x 150 mL). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting solid was dried overnight under vacuum to provide 28.49 g of *tert*-butyl (5-oxido-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl)carbamate as a brown solid.

Part F

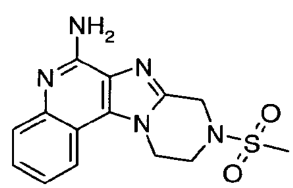
Concentrated ammonium hydroxide (160 mL) was added with vigorous stirring to a solution of *tert*-butyl (5-oxido-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl)carbamate (28.49 g, 83.7 mmol) in dichloromethane (300 mL). *p*-Toluenesulfonyl chloride (15.96 g, 83.7 mmol) was added in small portions over a period of five minutes, after which an analysis by HPLC indicated that the reaction was complete. The aqueous layer was then extracted with dichloromethane (3 x 150 mL), and the combined organic fractions were washed with 1% aqueous sodium carbonate (2 x 150 mL). The combined aqueous washings were extracted with dichloromethane (200 mL), and all organic fractions were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide *tert*-butyl (6-amino-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl)carbamate as a yellow solid.

Material from another run was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 99:1 to 85:15) to provide the product as a white powder.

Anal. Calcd for $C_{18}H_{21}N_5O_2$: C, 63.70; H, 6.24; N, 20.63. Found: C, 63.65; H, 6.51; N, 20.52.

Example 5

9-Methanesulfonyl-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine trifluoroacetate



Part A

Hydrogen chloride (300 mL of a 4 N solution in 1,4-dioxane) was added to a solution of *tert*-butyl (6-amino-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl)carbamate (34.74 g, 102.36 mmol) in dichloromethane (300 mL). The reaction was stirred overnight at ambient temperature and then concentrated under reduced pressure. The resulting solid was suspended in dichloromethane, isolated by filtration, and

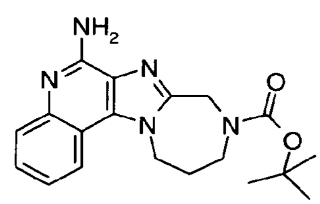
washed sequentially with dichloromethane, diethyl ether, hexane, and diethyl ether. The solid was then triturated with methanol and isolated by filtration to provide 11.58 g of 8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride as a white solid. The filtrate was concentrated under reduced pressure, dissolved in water, and precipitated with 1,4-dioxane to provide an additional 6.95 g of product.

Part B

Triethylamine (2.8 mL, 20.1 mmol) was added to a suspension of 8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (1.85 g, 6.71 mmol) in DMF (20 mL). The mixture was sonicated for ten minutes at 80 °C, and methanesulfonyl chloride (922 mg, 8.05 mmol) was slowly added. The mixture was stirred at ambient temperature overnight. After the solvent was removed under reduced pressure, the residue was combined with material from two other runs and ultimately purified by prep HPLC according to the method described above to provide 9-methanesulfonyl-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine trifluoroacetate as off-white needles, mp 242-243 °C.

Example 6

tert-Butyl (6-amino-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl)carbamate



Part A

4-Chloro-3-nitroquinoline (54.42 g, 260.9 mmol) was added to a solution of *tert*-butyl *N*-(3-aminopropyl)carbamate (50.0 g, 287 mmol) in anhydrous DMF (300 mL), and the reaction was stirred overnight at ambient temperature. The product was isolated as described in Part A of Example 4 to provide 84.55 g of *tert*-butyl [3-(3-nitroquinolin-4-ylamino)propyl]carbamate as a yellow solid.

Part B

A solution of *tert*-butyl [3-(3-nitroquinolin-4-ylamino)propyl]carbamate (50.0 g, 144 mmol) in 1,2-dichloroethane (450 mL) and 5% platinum on carbon (16.9 g, 86.6 mmol) were added to a Parr vessel, which was placed under hydrogen pressure (30 psi, 2.1 x 10^5 Pa) and shaken until the reaction was complete. The reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and the resulting solution was filtered to remove an insoluble impurity, washed sequentially with brine (3 x) and dilute aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 42.52 g of *tert*-butyl [3-(3-aminoquinolin-4-ylamino)propyl]carbamate.

Part C

Triethylamine (20.4 g, 202 mmol) was added to a solution of *tert*-butyl [3-(3-aminoquinolin-4-ylamino)propyl]carbamate (42.52 g, 134.4 mmol) in dichloromethane (500 mL). Chloroacetyl chloride (16.7 g, 148 mmol) was added dropwise, and the reaction was stirred overnight at ambient temperature. The reaction mixture was filtered to remove a solid; the filtrate was concentrated under reduced pressure and mixed with ethyl acetate. The resulting mixture was filtered to remove a solid, washed sequentially with brine (3 x) and dilute aqueous sodium bicarbonate, concentrated under reduced pressure, and dried under high vacuum to provide 41.9 g of *tert*-butyl [3-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate.

Part D

A modification of the method described in Part D of Example 4 was used to treat *tert*-butyl [3-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (36.76 g, 98.1 mmol) with potassium *tert*-butoxide (107.9 mL of a 1 M solution in THF). Following the work-up procedure, the product was mixed with ethyl acetate. The resulting mixture was filtered to remove a solid, and the filtrate was concentrated under reduced pressure to provide 30.0 g of *tert*-butyl (9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl)carbamate.

Part E

The general method described in Part E of Example 4 was used to treat *tert*-butyl 7 (30.0 g, 88.6 mmol) with mCPBA (23.8 g of 77% pure material, 138 mmol) to provide *tert*-butyl (5-oxido-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl)carbamate. The product was not dried over magnesium sulfate but was dried under high vacuum overnight.

Part F

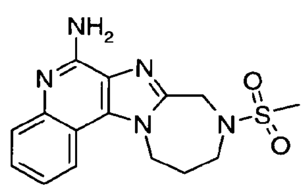
The general method described in Part F of Example 4 was used to aminate the material from Part E with ammonium hydroxide (170 mL) and *p*-toluenesulfonyl chloride (16.92 g, 88.74 mmol) to provide 28.44 g of *tert*-butyl (6-amino-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl)carbamate.

Material from another run was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 99:1 to 85:15) to provide the product as a white powder.

Anal. Calcd for $C_{19}H_{23}N_5O_2$: C, 64.57; H, 6.56; N, 19.82. Found: C, 64.29; H, 6.82; N, 19.54.

Example 7

9-Methanesulfonyl-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine trifluoroacetate



Part A

The general method described in Part A of Example 5 was used to deprotect *tert*-butyl (6-amino-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl)carbamate (28.44 g, 80.47 mmol). A precipitate was present at the end of the reaction and was isolated by filtration. The solid was dissolved in a small amount of water, precipitated with 1,4-dioxane, isolated by filtration, and dried for two days in a vacuum

oven at 75 °C to provide 17.04 g of the 9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride.

Part B

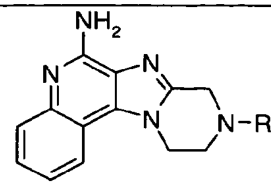
The general methods described in Part B of Example 5 were used to prepare 9-methanesulfonyl-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine trifluoroacetate, which was isolated as white needles, mp 250-250.9 °C.

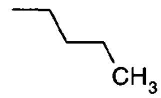
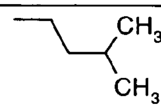
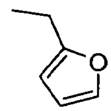
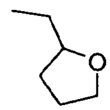
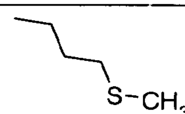
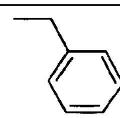
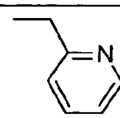
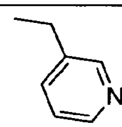
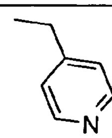
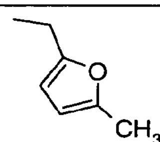
Anal. Calcd for $C_{15}H_{17}N_5O_2S \bullet 1.10\ C_2HF_3O_2 \bullet 0.30\ H_2O$: C, 44.69; H, 4.08; N, 15.15. Found: C, 45.05; H, 3.76; N, 15.22.

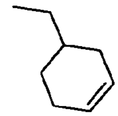
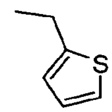
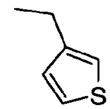
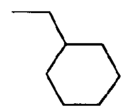
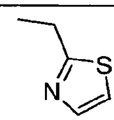
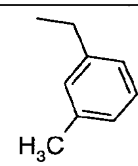
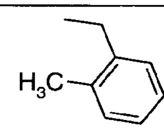
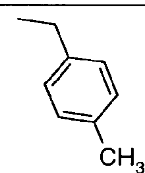
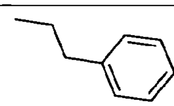
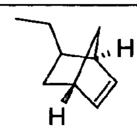
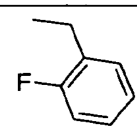
Examples 8-73

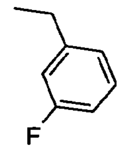
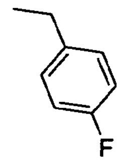
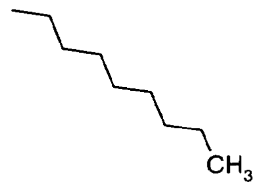
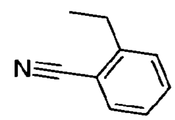
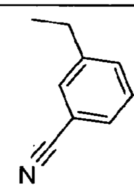
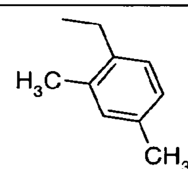
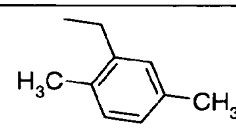
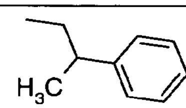
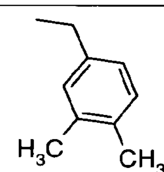
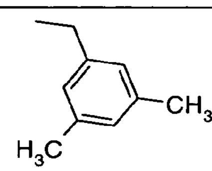
The aldehyde (0.125 mmol) indicated in the table below was added to a solution of 8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (31.25 mg, 0.100 mmol) and *N,N*-diisopropylethylamine (0.035 mL, 0.20 mmol) in anhydrous DMF (2 mL) in a test tube. The test tube was capped and shaken for 15 minutes. Borane-pyridine complex (13 µL, 0.128 mmol) was added, and the reaction was shaken overnight. The solvent was removed by vacuum centrifugation. The compounds were purified by prep HPLC according to the method described above. The table below shows aldehyde used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

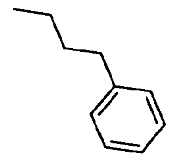
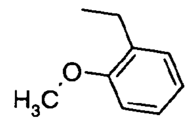
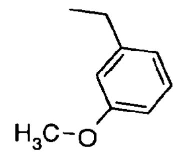
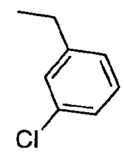
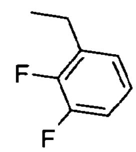
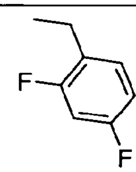
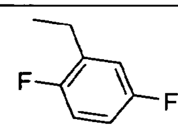
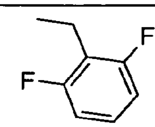
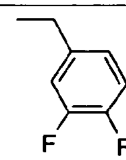
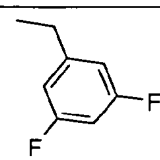
Examples 8-73

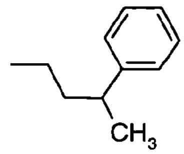
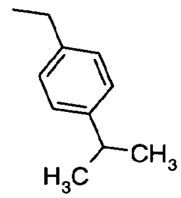
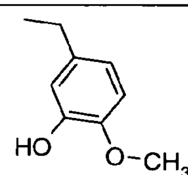
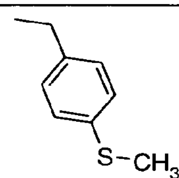
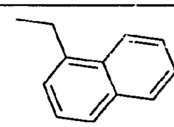
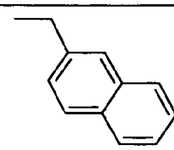
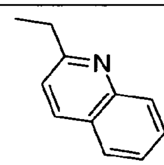
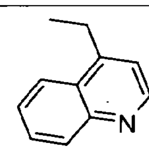
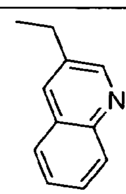


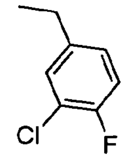
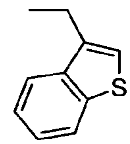
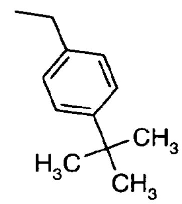
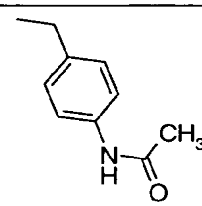
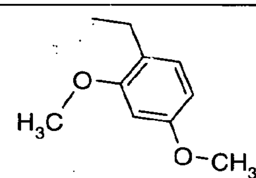
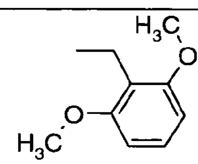
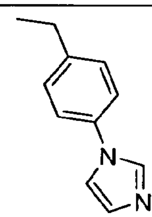
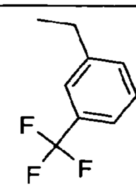
Example	Aldehyde	R	Measured Mass (M+H)
8	Butyraldehyde		296.1886
9	Isovaleraldehyde		310.2028
10	Furfural		320.1519
11	Tetrahydrofuran-3-carboxaldehyde		324.1843
12	3-(Methylthio)propionaldehyde		328.1619
13	Benzaldehyde		330.1751
14	2-Pyridinecarboxaldehyde		331.1684
15	3-Pyridinecarboxaldehyde		331.1691
16	4-Pyridinecarboxaldehyde		331.1670
17	5-Methylfurfural		334.1698

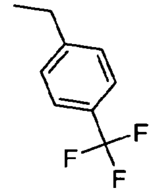
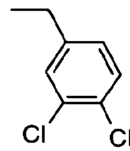
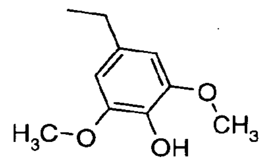
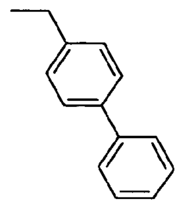
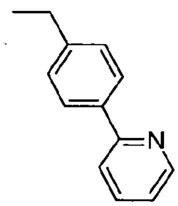
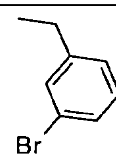
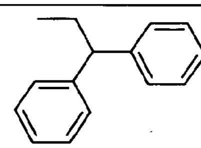
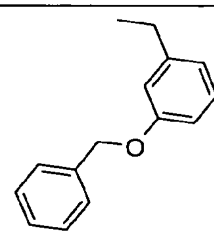
18	1,2,3,6-Tetrahydrobenzaldehyde		334.2045
19	2-Thiophenecarboxaldehyde		336.1305
20	3-Thiophenecarboxaldehyde		336.1279
21	Cyclohexanecarboxaldehyde		336.2178
22	Thiazole-2-carboxaldehyde		337.1244
23	*m*-Tolualdehyde		344.1898
24	*o*-Tolualdehyde		344.1885
25	*p*-Tolualdehyde		344.1895
26	Phenylacetaldehyde		344.1908
27	5-Norbornene-2-carboxaldehyde		346.2049
28	2-Fluorobenzaldehyde		348.1633

29	3-Fluorobenzaldehyde		348.1656
30	4-Fluorobenzaldehyde		348.1638
31	Octanal		352.2493
32	2-Cyanobenzaldehyde		355.1696
33	3-Cyanobenzaldehyde		355.1700
34	2,4-Dimethylbenzaldehyde		358.2039
35	2,5-Dimethylbenzaldehyde		358.2057
36	2-Phenylpropionaldehyde		358.2044
37	3,4-Dimethylbenzaldehyde		358.2041
38	3,5-Dimethylbenzaldehyde		358.2042

39	3-Phenylpropionaldehyde		358.2040
40	2-Methoxybenzaldehyde		360.1855
41	3-Methoxybenzaldehyde		360.1830
42	3-Chlorobenzaldehyde		364.1318
43	2,3-Difluorobenzaldehyde		366.1544
44	2,4-Difluorobenzaldehyde		366.1559
45	2,5-Difluorobenzaldehyde		366.1544
46	2,6-Difluorobenzaldehyde		366.1552
47	3,4-Difluorobenzaldehyde		366.1526
48	3,5-Difluorobenzaldehyde		366.1559

49	3-Phenylbutyraldehyde		372.2213
50	Cuminaldehyde		372.2210
51	3-Hydroxy-4-methoxybenzaldehyde		376.1783
52	4-(Methylthio)benzaldehyde		376.1618
53	1-Naphthaldehyde		380.1891
54	2-Naphthaldehyde		380.1910
55	2-Quinolinecarboxaldehyde		381.1857
56	4-Quinolinecarboxaldehyde		381.1861
57	Quinoline-3-carboxaldehyde		381.1850

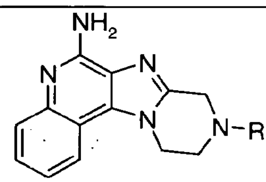
58	3-Chloro-4-fluorobenzaldehyde		382.1216
59	Thianaphthene-3-carboxaldehyde		386.1435
60	4-*tert*-Butylbenzaldehyde		386.2370
61	4-Acetamidobenzaldehyde		387.1960
62	2,4-Dimethoxybenzaldehyde		390.1944
63	2,6-Dimethoxybenzaldehyde		390.1940
64	4-(1*H*-Imidazol-1-yl)benzaldehyde		396.1953
65	3-(Trifluoromethyl)benzaldehyde		398.1613

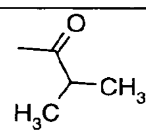
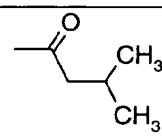
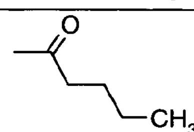
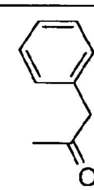
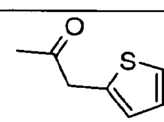
66	4-(Trifluoromethyl)benzaldehyde		398.1630
67	3,4-Dichlorobenzaldehyde		398.0961
68	Syringaldehyde		406.1916
69	4-Biphenylcarboxaldehyde		406.2052
70	4-(2-Pyridyl)benzaldehyde		407.1984
71	3-Bromobenzaldehyde		408.0809
72	Diphenylacetaldehyde		420.2213
73	3-Benzyloxybenzaldehyde		436.2172

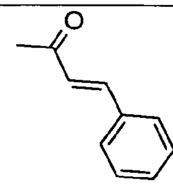
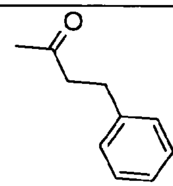
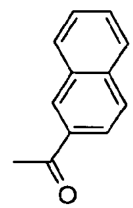
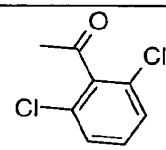
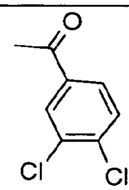
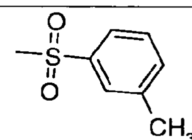
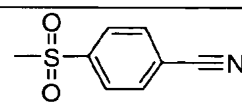
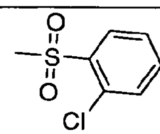
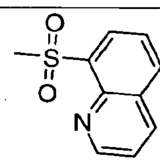
Examples 74-113

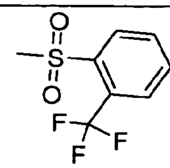
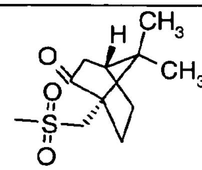
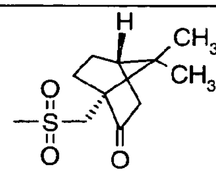
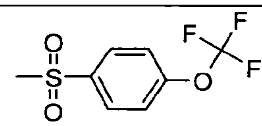
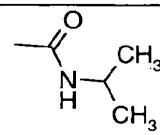
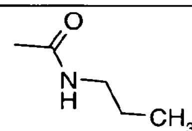
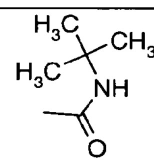
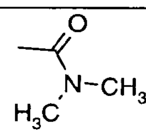
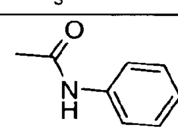
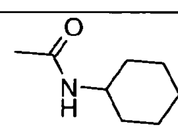
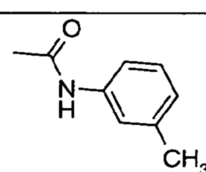
The reagent (0.11 mmol) indicated in the table below was added to a solution of 8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (24 mg, 0.077 mmol) and *N,N*-diisopropylethylamine (0.070 mL, 0.40 mmol) in anhydrous DMF (2 mL) in a test tube. The test tube was capped and shaken overnight. One drop of deionized water was added to each test tube, and the solvent was removed by vacuum centrifugation. The compounds were purified by prep HPLC using the method described above. The table below shows the acid chloride, sulfonyl chloride, isocyanate, or carbamoyl chloride used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

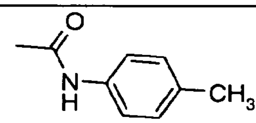
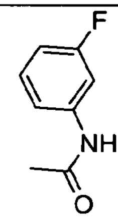
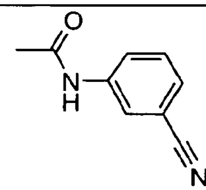
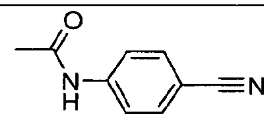
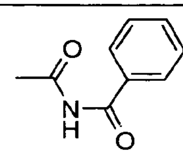
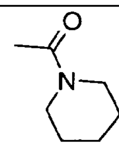
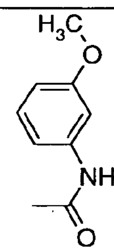
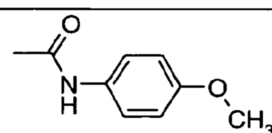
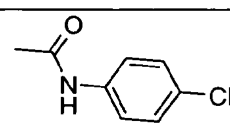
Examples 74-113

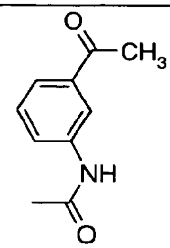
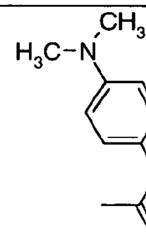
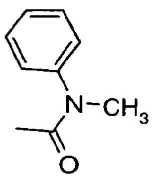
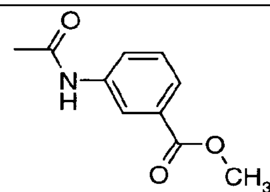
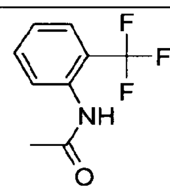
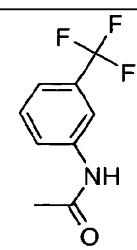


Example	Reagent	R	Measured Mass (M+H)
74	Isobutyryl chloride		310.1672
75	Isovaleryl chloride		324.1825
76	Pentanoyl chloride		324.1813
77	Phenylacetyl chloride		358.1682
78	Thiophene-2-acetyl chloride		364.2162

79	Cinnamoyl chloride		370.1676
80	Hydrocinnamoyl chloride		372.1840
81	2-Naphthoyl chloride		394.1695
82	2,6-Dichlorobenzoyl chloride		412.0770
83	3,4-Dichlorobenzoyl chloride		412.0736
84	*m*-Toluenesulfonyl chloride		394.1346
85	4-Cyanobenzenesulfonyl chloride		405.1173
86	2-Chlorobenzenesulfonyl chloride		414.0786
87	8-Quinolinesulfonyl chloride		431.1279

88	2-(Trifluoromethyl)benzenesulfonyl chloride		448.1073
89	(-)-Camphor-10-sulfonyl chloride		454.1919
90	D-(+)-10-Camphorsulfonyl chloride		454.1917
91	4-(Trifluoromethoxy) benzenesulfonyl chloride		464.1021
92	Isopropyl isocyanate		325.1791
93	*n*-Propyl isocyanate		325.1802
94	*tert*-Butyl isocyanate		339.1955
95	Dimethylcarbamoyl chloride		311.1600
96	Phenyl isocyanate		359.1635
97	Cyclohexane isocyanate		365.2094
98	*m*-Tolyl isocyanate		373.1790

99	*p*-Tolyl isocyanate		373.1812
100	3-Fluorophenyl isocyanate		377.1559
101	3-Cyanophenyl isocyanate		384.1573
102	4-Cyanophenyl isocyanate		384.1605
103	Benzoyl isocyanate		387.1575
104	1-Piperidinecarbonyl chloride		351.1909
105	3-Methoxyphenyl isocyanate		389.1732
106	4-Methoxyphenyl isocyanate		389.1761
107	4-Chlorophenyl isocyanate		393.1261

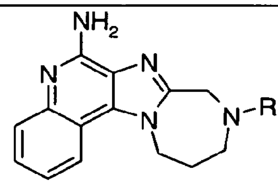
108	3-Acetylphenyl isocyanate		401.1763
109	4-(Dimethylamino)phenyl isocyanate		402.2050
110	*N*-Methyl-*N*-phenylcarbamoyl chloride		373.1764
111	Methyl 3-isocyanatobenzoate		417.1692
112	2-(Trifluoromethyl)phenyl isocyanate		427.1511
113	3-(Trifluoromethyl)phenyl isocyanate		427.1479

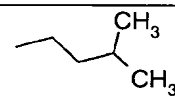
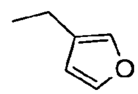
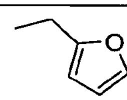
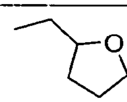
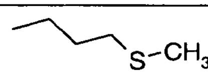
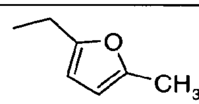
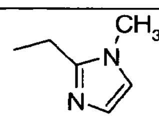
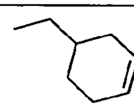
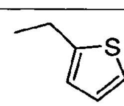
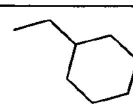
Examples 114-188

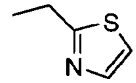
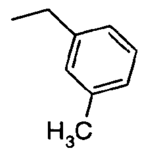
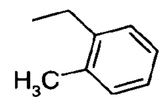
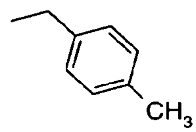
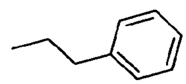
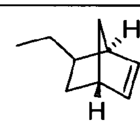
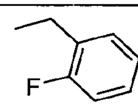
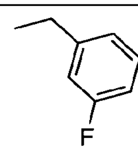
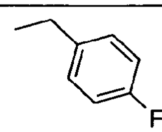
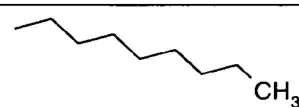
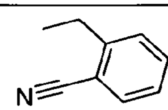
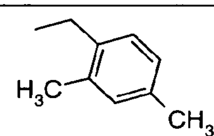
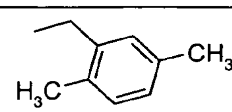
The general method described in Examples 8-73 was used to treat 9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (32.3 mg, 0.099 mmol) with the aldehyde (0.125 mmol) indicated in the table below. The compounds were purified by prep HPLC using the method described above. The table

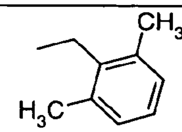
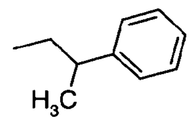
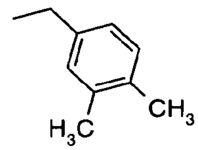
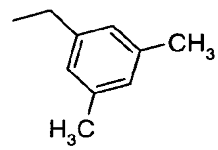
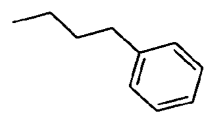
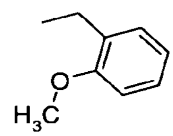
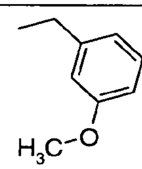
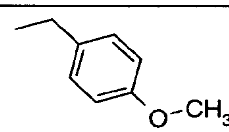
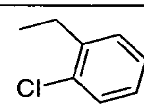
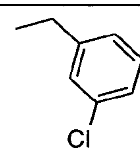
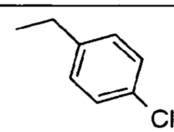
below shows the aldehyde used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

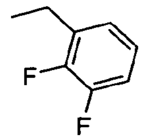
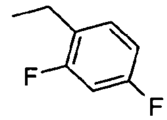
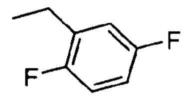
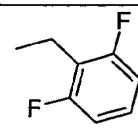
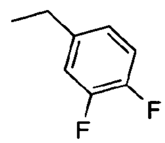
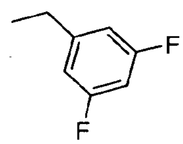
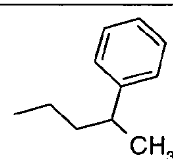
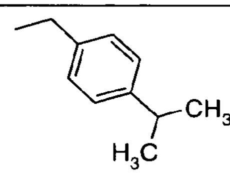
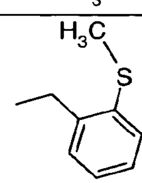
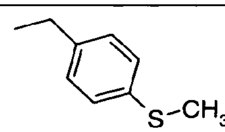
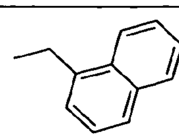
Examples 114-188

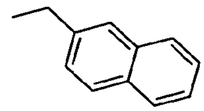
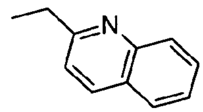
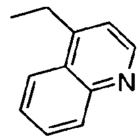
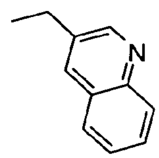
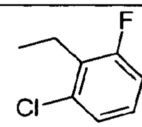
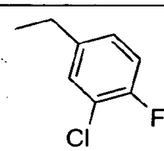
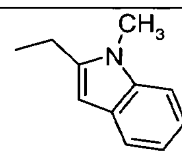
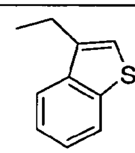
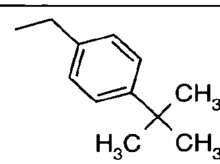
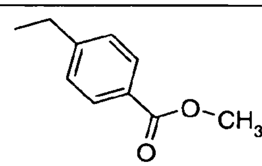


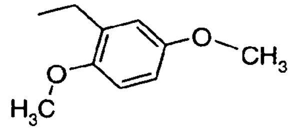
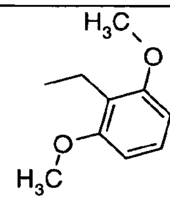
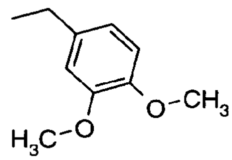
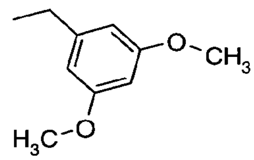
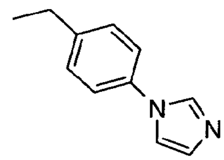
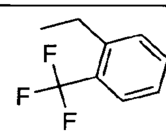
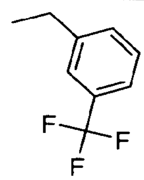
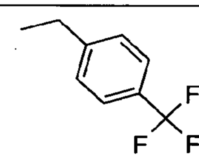
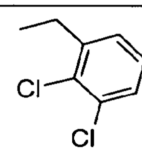
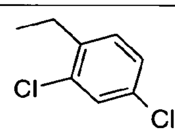
Example	Aldehyde	R	Measured Mass (M+H)
114	Isovaleraldehyde		324.2216
115	3-Furaldehyde		334.1687
116	Furfural		334.1680
117	Tetrahydrofuran-3-carboxaldehyde		338.2001
118	3-(Methylthio)propionaldehyde		342.1762
119	5-Methylfurfural		348.1849
120	1-Methyl-2-imidazolecarboxaldehyde		348.1934
121	1,2,3,6-Tetrahydrobenzaldehyde		348.2169
122	2-Thiophenecarboxaldehyde		350.1443
123	Cyclohexanecarboxaldehyde		350.2365

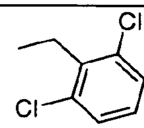
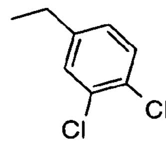
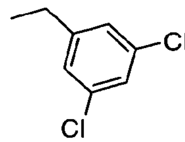
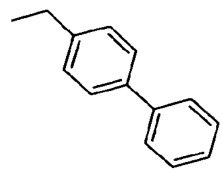
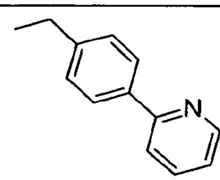
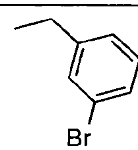
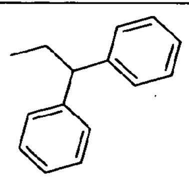
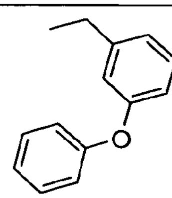
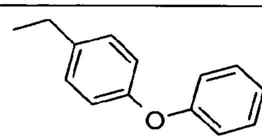
124	Thiazole-2-carboxaldehyde		351.1413
125	*m*-Tolualdehyde		358.2049
126	*o*-Tolualdehyde		358.2057
127	*p*-Tolualdehyde		358.2039
128	Phenylacetaldehyde		358.2029
129	5-Norbornene-2-carboxaldehyde		360.2199
130	2-Fluorobenzaldehyde		362.1790
131	3-Fluorobenzaldehyde		362.1784
132	4-Fluorobenzaldehyde		362.1775
133	Octanal		366.2640
134	2-Cyanobenzaldehyde		369.1852
135	2,4-Dimethylbenzaldehyde		372.2216
136	2,5-Dimethylbenzaldehyde		372.2185

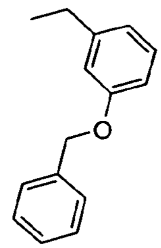
137	2,6-Dimethylbenzaldehyde		372.2202
138	2-Phenylpropionaldehyde		372.2208
139	3,4-Dimethylbenzaldehyde		372.2206
140	3,5-Dimethylbenzaldehyde		372.2205
141	3-Phenylpropionaldehyde		372.2208
142	2-Methoxybenzaldehyde		374.1985
143	3-Methoxybenzaldehyde		374.2007
144	*p*-Anisaldehyde		374.1991
145	2-Chlorobenzaldehyde		378.1490
146	3-Chlorobenzaldehyde		378.1509
147	4-Chlorobenzaldehyde		378.1519

148	2,3-Difluorobenzaldehyde		380.1683
149	2,4-Difluorobenzaldehyde		380.1696
150	2,4-Difluorobenzaldehyde		380.1691
151	2,6-Difluorobenzaldehyde		380.1713
152	3,4-Difluorobenzaldehyde		380.1695
153	3,5-Difluorobenzaldehyde		380.1693
154	3-Phenylbutyraldehyde		386.2366
155	Cuminaldehyde		386.2386
156	2-(Methylthio)benzaldehyde		390.1791
157	4-(Methylthio)benzaldehyde		390.1776
158	1-Naphthaldehyde		394.2055

159	2-Naphthaldehyde		394.2041
160	2-Quinolinecarboxaldehyde		395.2013
161	4-Quinolinecarboxaldehyde		395.2016
162	Quinoline-3-carboxaldehyde		395.2010
163	2-Chloro-6-fluorobenzaldehyde		396.1422
164	3-Chloro-4-fluorobenzaldehyde		396.1386
165	1-Methylindole-2-carboxaldehyde		397.2133
166	Thianaphthene-3-carboxaldehyde		400.1615
167	4-*tert*-Butylbenzaldehyde		400.2468
168	Methyl 4-formylbenzoate		402.1954

169	2,5-Dimethoxybenzaldehyde		404.2111
170	2,6-Dimethoxybenzaldehyde		404.2102
171	3,4-Dimethoxybenzaldehyde		404.2094
172	3,5-Dimethoxybenzaldehyde		404.2091
173	4-(1*H*-Imidazol-1-yl)benzaldehyde		410.2101
174	2-(Trifluoromethyl)benzaldehyde		412.1722
175	3-(Trifluoromethyl)benzaldehyde		412.1757
176	4-(Trifluoromethyl)benzaldehyde		412.1757
177	2,3-Dichlorobenzaldehyde		412.1117
178	2,4-Dichlorobenzaldehyde		412.1100

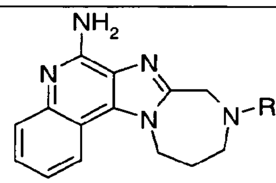
179	2,6-Dichlorobenzaldehyde		412.1117
180	3,4-Dichlorobenzaldehyde		412.1131
181	3,5-Dichlorobenzaldehyde		412.1116
182	4-Biphenylcarboxaldehyde		420.2209
183	4-(2-Pyridyl)benzaldehyde		421.2167
184	3-Bromobenzaldehyde		422.0999
185	Diphenylacetaldehyde		434.2369
186	3-Phenoxybenzaldehyde		436.2137
187	4-Phenoxybenzaldehyde		436.2163

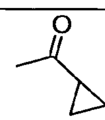
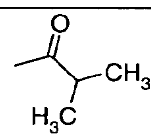
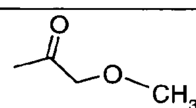
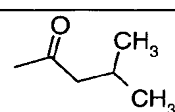
188	3-Benzyloxybenzaldehyde		450.2297

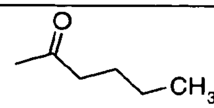
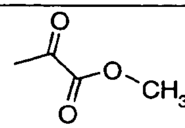
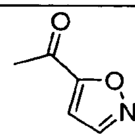
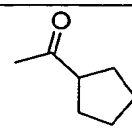
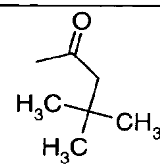
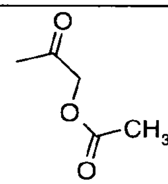
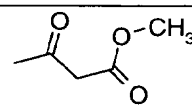
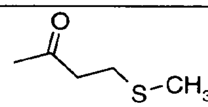
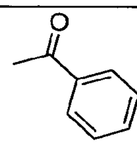
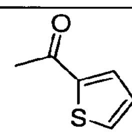
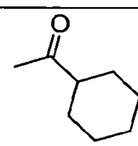
Example 189-329

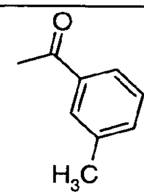
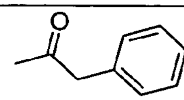
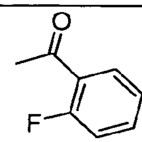
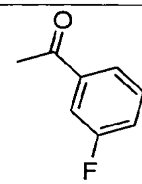
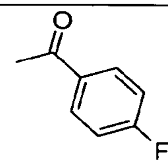
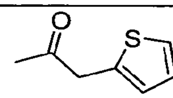
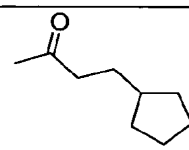
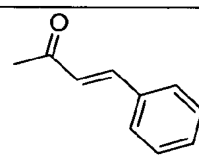
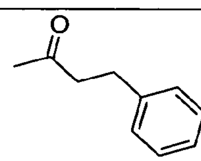
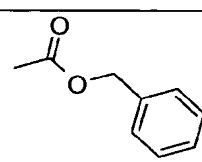
The general method described in Examples 74-113 was used to treat 9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (32.5 mg, 0.100 mmol) with *N,N*-diisopropylethylamine (0.0525 mL, 0.30 mmol) and the reagent (0.108 mmol) indicated in the table below. The compounds were purified by prep HPLC using the method described above. The table below shows the acid chloride, sulfonyl chloride, isocyanate, carbamoyl chloride, or sulfamoyl chloride used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

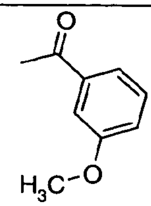
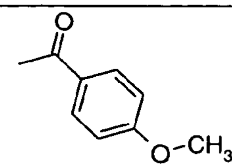
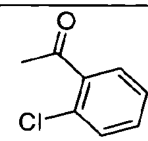
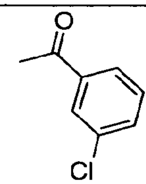
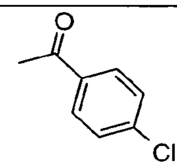
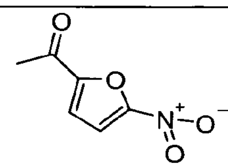
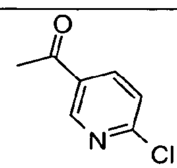
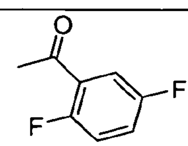
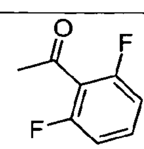
Examples 189-329

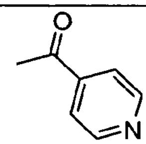
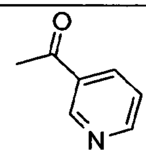
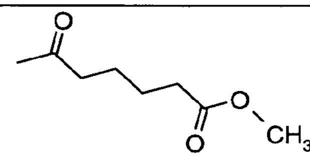
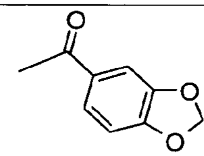
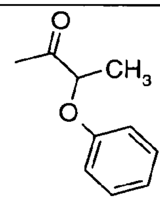
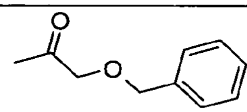
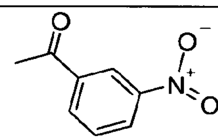
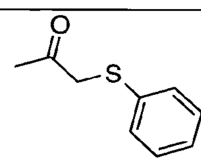
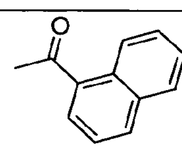
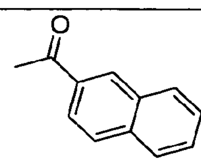


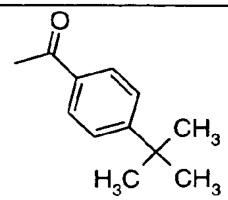
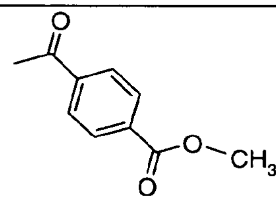
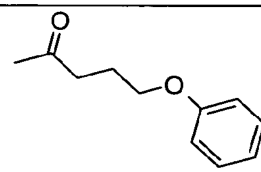
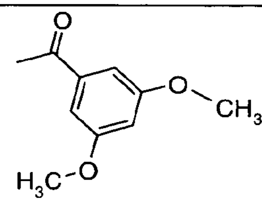
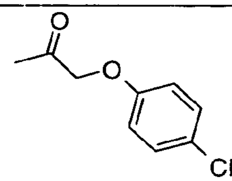
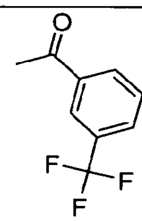
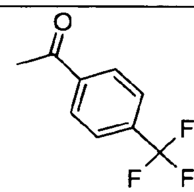
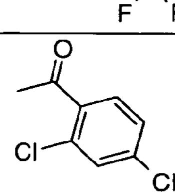
Example	Reagent	R	Measured Mass (M+H)
189	Cyclopropanecarbonyl chloride		322.1653
190	Isobutyryl chloride		324.1812
191	Methoxyacetyl chloride		326.1616
192	Isovaleryl chloride		338.1970

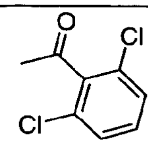
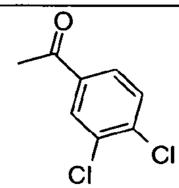
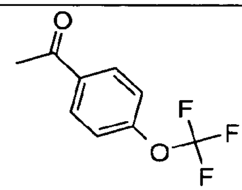
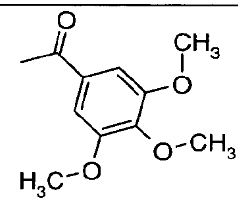
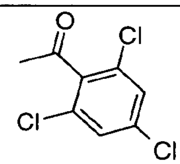
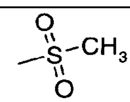
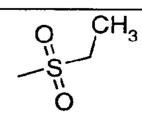
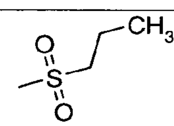
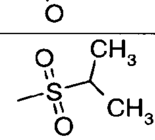
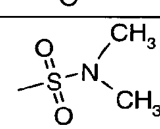
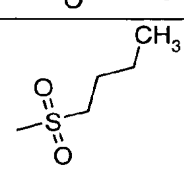
193	Pentanoyl chloride		338.1986
194	Methyl oxalyl chloride		340.1394
195	Isoxazole-5-carbonyl chloride		349.1419
196	Cyclopentanecarbonyl chloride		350.1971
197	*tert*-Butylacetyl chloride		352.2117
198	Acetoxyacetyl chloride		354.1550
199	Methyl malonyl chloride		354.1555
200	3-Methylthiopropionyl chloride		356.1541
201	Benzoyl chloride		358.1659
202	Thiophene-2-carbonyl chloride		364.1246
203	Cyclohexanecarbonyl chloride		364.2122

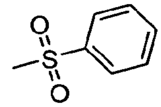
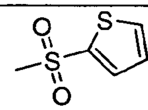
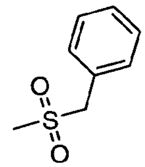
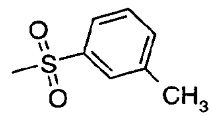
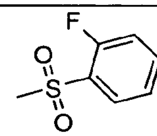
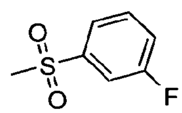
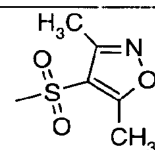
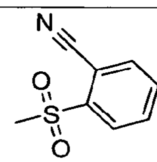
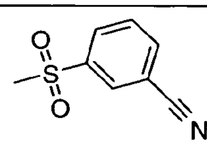
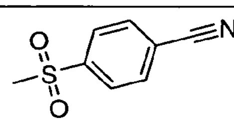
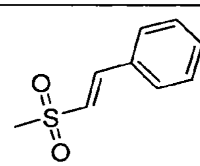
204	*m*-Toluoyl chloride		372.1835
205	Phenylacetyl chloride		372.1830
206	2-Fluorobenzoyl chloride		376.1570
207	3-Fluorobenzoyl chloride		376.1579
208	4-Fluorobenzoyl chloride		376.1573
209	2-Thiopheneacetyl chloride		378.1382
210	3-Cyclopentylpropionyl chloride		378.2298
211	Cinnamoyl chloride		384.1814
212	Hydrocinnamoyl chloride		386.1988
213	Benzyl chloroformate		388.1793

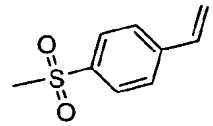
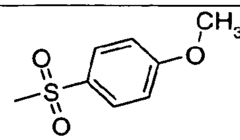
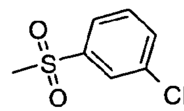
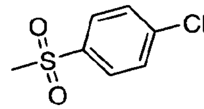
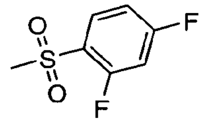
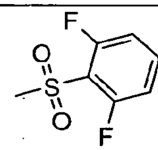
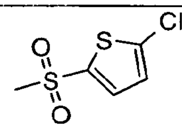
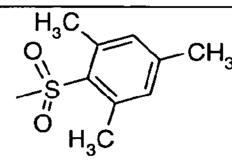
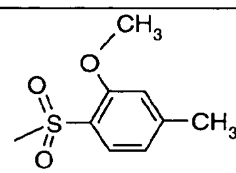
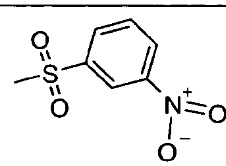
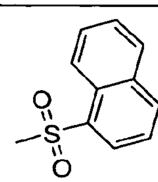
214	*m*-Anisoyl chloride		388.1752
215	*p*-Anisoyl chloride		388.1808
216	2-Chlorobenzoyl chloride		392.1268
217	3-Chlorobenzoyl chloride		392.1276
218	4-Chlorobenzoyl chloride		392.1291
219	5-Nitro-2-furoyl chloride		393.1317
220	6-Chloronicotinyl chloride		393.1237
221	2,5-Difluorobenzoyl chloride		394.1472
222	2,6-Difluorobenzoyl chloride		394.1468

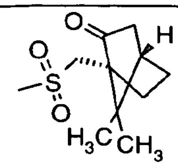
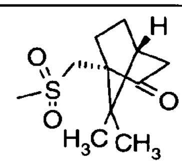
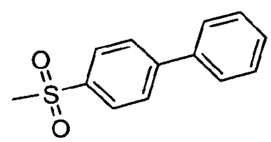
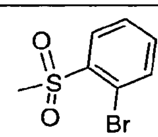
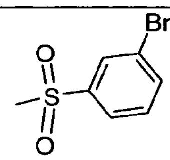
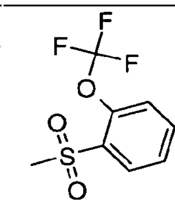
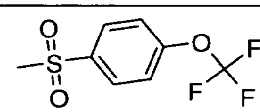
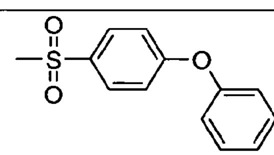
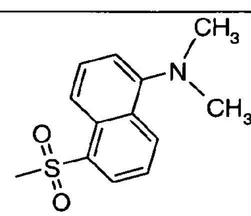
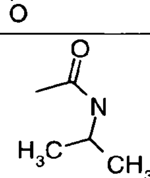
223	Isonicotinoyl chloride hydrochloride		359.1619
224	Nicotinoyl chloride hydrochloride		359.1613
225	Methyl adipoyl chloride		396.2035
226	3,4-Methylenedioxybenzoyl chloride		402.1560
227	2-Phenoxypropionyl chloride		402.1921
228	Benzyloxyacetyl chloride		402.1928
229	3-Nitrobenzoyl chloride		403.1527
230	(Phenylthio)acetyl chloride		404.1550
231	1-Naphthoyl chloride		408.1833
232	2-Naphthoyl chloride		408.1820

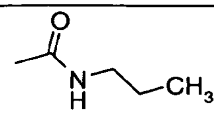
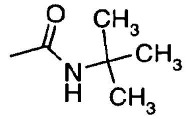
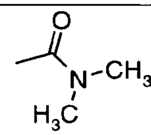
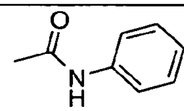
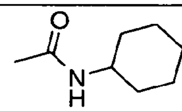
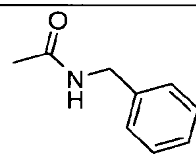
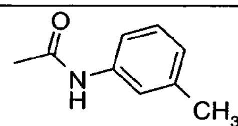
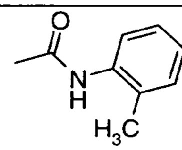
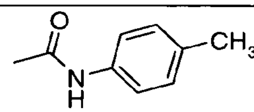
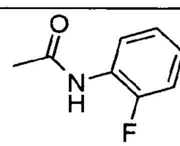
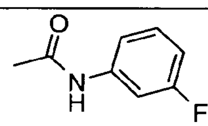
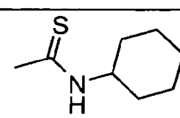
233	4-*tert*-Butylbenzoyl chloride		414.2271
234	Methyl 4-chlorocarbonyl benzoate		416.1727
235	4-Phenoxybutyryl chloride		416.2069
236	3,5-Dimethoxybenzoyl chloride		418.1880
237	4-Chlorophenoxyacetyl chloride		422.1409
238	3-(Trifluoromethyl)benzoyl chloride		426.1581
239	4-(Trifluoromethyl)benzoyl chloride		426.1558
240	2,4-Dichlorobenzoyl chloride		426.0907

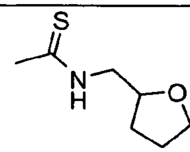
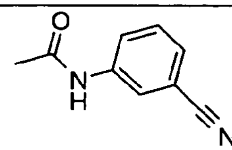
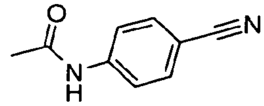
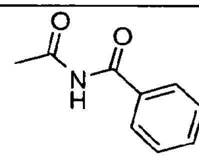
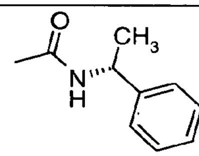
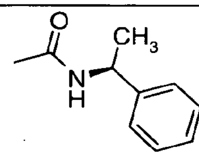
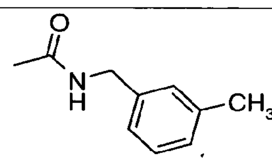
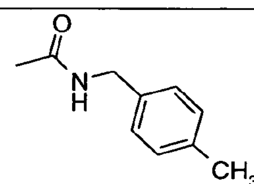
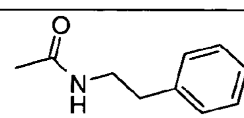
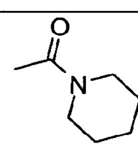
241	2,6-Dichlorobenzoyl chloride		426.0891
242	3,4-Dichlorobenzoyl chloride		426.0871
243	4-(Trifluoromethoxy)benzoyl chloride		442.1489
244	3,4,5-Trimethoxybenzoyl chloride		448.2001
245	2,4,6-Trichlorobenzoyl chloride		460.0494
246	Methanesulfonyl chloride		332.1168
247	Ethanesulfonyl chloride		346.1333
248	1-Propanesulfonyl chloride		360.1497
249	Isopropylsulfonyl chloride		360.1490
250	Dimethylsulfamoyl chloride		361.1455
251	1-Butanesulfonyl chloride		374.1654

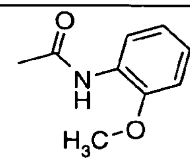
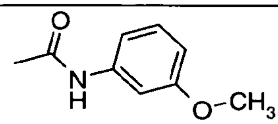
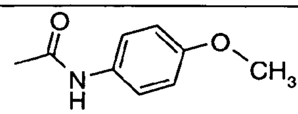
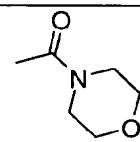
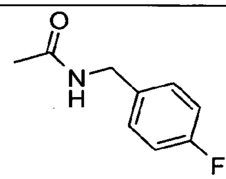
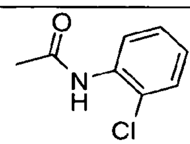
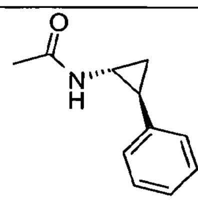
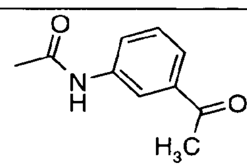
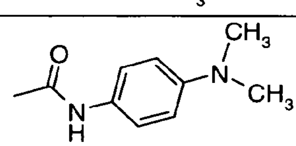
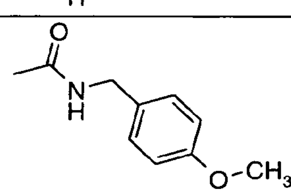
252	Benzenesulfonyl chloride		394.1320
253	2-Thiophenesulfonyl chloride		400.0913
254	α-Toluenesulfonyl chloride		408.1497
255	*m*-Toluenesulfonyl chloride		408.1502
256	2-Fluorobenzenesulfonyl chloride		412.1233
257	3-Fluorobenzenesulfonyl chloride		412.1238
258	3,5-Dimethylisoxazole-4-sulfonyl chloride		413.1385
259	2-Cyanobenzenesulfonyl chloride		419.1289
260	3-Cyanobenzenesulfonyl chloride		419.1307
261	4-Cyanobenzenesulfonyl chloride		419.1302
262	β-Styrenesulfonyl chloride		420.1479

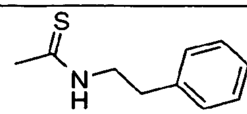
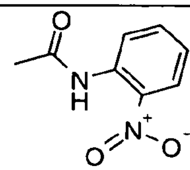
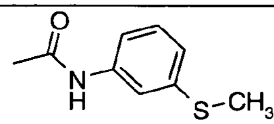
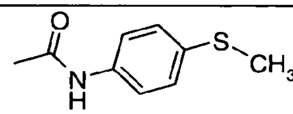
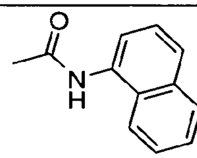
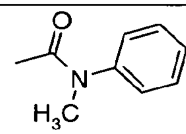
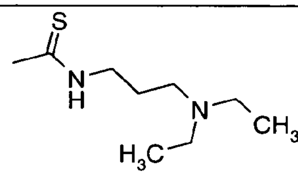
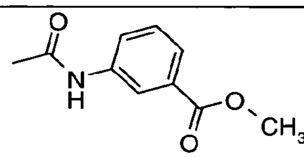
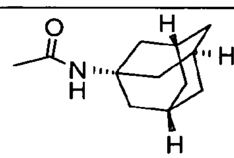
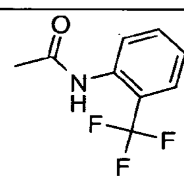
263	*p*-Styrenesulfonyl chloride		420.1496
264	4-Methoxybenzenesulfonyl chloride		424.1448
265	3-Chlorobenzenesulfonyl chloride		428.0941
266	4-Chlorobenzenesulfonyl chloride		428.0944
267	2,4-Difluorobenzenesulfonyl chloride		430.1145
268	2,6-Difluorobenzenesulfonyl chloride		430.1121
269	5-Chlorothiophene-2-sulfonyl chloride		434.0519
270	2-Mesitylenesulfonyl chloride		436.1814
271	2-Methoxy-4-methylbenzenesulfonyl chloride		438.1613
272	3-Nitrobenzenesulfonyl chloride		439.1199
273	1-Naphthalenesulfonyl chloride		444.1506

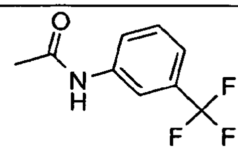
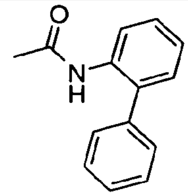
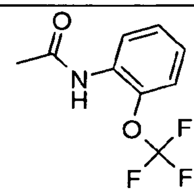
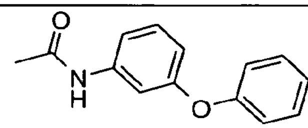
274	(-)-Camphor-10-sulfonyl chloride		468.2098
275	D-(+)-10-Camphorsulfonyl chloride		468.2106
276	4-Biphenylsulfonyl chloride		470.1639
277	2-Bromobenzenesulfonyl chloride		472.0459
278	3-Bromobenzenesulfonyl chloride		472.0471
279	2-(Trifluoromethoxy) benzenesulfonyl chloride		478.1171
280	4-(Trifluoromethoxy) benzenesulfonyl chloride		478.1155
281	4-Phenoxybenzenesulfonyl chloride		486.1613
282	Dansyl chloride		487.1920
283	Isopropyl isocyanate		339.1965

284	*n*-Propyl isocyanate		339.1947
285	*tert*-Butyl isocyanate		353.2108
286	Dimethylcarbamoyl chloride		325.1804
287	Phenyl isocyanate		373.1803
288	Cyclohexane isocyanate		379.2275
289	Benzyl isocyanate		387.1943
290	*m*-Tolyl isocyanate		387.1951
291	*o*-Tolyl isocyanate		387.1937
292	*p*-Tolyl isocyanate		387.1959
293	2-Fluorophenyl isocyanate		391.1706
294	3-Fluorophenyl isocyanate		391.1705
295	Cyclohexyl isothiocyanate		395.2041

296	2-Tetrahydrofurfuryl isothiocyanate		397.1836
297	3-Cyanophenyl isocyanate		398.1749
298	4-Cyanophenyl isocyanate		398.1752
299	Benzoyl isocyanate		401.1750
300	(R)-(+)-1-Phenylethyl isocyanate		401.2080
301	(S)-(-)-1-Phenylethyl isocyanate		401.2078
302	3-Methylbenzyl isocyanate		401.2122
303	4-Methylbenzyl isocyanate		401.2096
304	Phenethyl isocyanate		401.2127
305	1-Piperidinecarbonyl chloride		365.2122

306	2-Methoxyphenyl isocyanate		403.1877
307	3-Methoxyphenyl isocyanate		403.1902
308	4-Methoxyphenyl isocyanate		403.1908
309	Morpholine-4-carbonyl chloride		367.1911
310	4-Fluorobenzyl isocyanate		405.1851
311	2-Chlorophenyl isocyanate		407.1408
312	*trans*-2-Phenylcyclopropyl isocyanate		413.2106
313	3-Acetylphenyl isocyanate		415.1899
314	4-(Dimethylamino)phenyl isocyanate		416.2213
315	4-Methoxybenzyl isocyanate		417.2069

316	Phenethyl isothiocyanate		417.1895
317	2-Nitrophenyl isocyanate		418.1662
318	3-(Methylthio)phenyl isocyanate		419.1671
319	4-(Methylthio)phenyl isocyanate		419.1695
320	1-Naphthyl isocyanate		423.1969
321	*N*-Methyl-*N*-phenylcarbamoyl chloride		387.1961
322	3-(Diethylamino)propyl isothiocyanate		426.2465
323	Methyl 3-isocyanatobenzoate		431.1852
324	1-Adamantyl isocyanate		431.2549
325	2-(Trifluoromethyl)phenyl isocyanate		441.1647

326	3-(Trifluoromethyl)phenyl isocyanate		441.1679
327	2-Biphenylyl isocyanate		449.2090
328	2-(Trifluoromethoxy)phenyl isocyanate		457.1633
329	3-Phenoxyphenyl isocyanate		465.2073

Examples 330-362

Part A

mCPBA (3.89 g of 77% pure material, 17.36 mmol) was added to a solution of *tert*-butyl [11-(*tert*-butyldimethylsilanyloxy)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl]carbamate (4.07 g, 8.68 mol) in chloroform, and the reaction was stirred for 30 minutes at ambient temperature. Additional mCPBA (0.5 equivalent) was added, and the reaction was stirred for four hours. Ammonium hydroxide (50 mL) was added with vigorous stirring, and after ten minutes, *p*-toluenesulfonyl chloride (1.82 g, 9.55 mmol) was added. The reaction was stirred overnight at ambient temperature and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting sequentially with 98.5:1:0.5 and 89:10:1 dichloromethane:methanol:ammonium hydroxide), and the resulting product was dried under high vacuum to provide 2.25 g of *tert*-butyl [6-amino-11-(*tert*-butyldimethylsilanyloxy)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl]carbamate.

Part B

Hydrochloric acid (75 mL of a 4 N solution in 1,4-dioxane) was added to *tert*-butyl [6-amino-11-(*tert*-butyldimethylsilanyloxy)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-9-yl]carbamate (2.15 g, 4.45 mmol), and the reaction was stirred for four hours at ambient temperature and then concentrated under reduced pressure. The residue was washed with dichloromethane and dried overnight under high vacuum to provide 930 mg of 11-(*tert*-butyldimethylsilanyloxy)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride as a light brown powder.

Part C

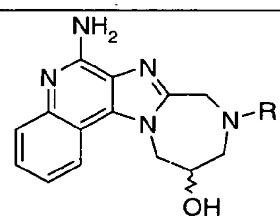
The reagent (0.11 mmol) indicated in the table below was added to a solution of 11-(*tert*-butyldimethylsilanyloxy)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (24 mg, 0.077 mmol) and *N,N*-diisopropylethylamine (0.0225 mL, 0.13 mmol) in chloroform (1 mL) in a test tube. For Examples 330-348, the test tube was capped and shaken overnight at ambient temperature. For Examples 349-362, the test tube was capped, heated at 50 °C for four hours, and then shaken overnight at ambient temperature. The reaction mixtures were separated by solid-supported liquid-liquid extraction according to the following procedure. Each reaction was loaded onto diatomaceous earth that had been treated with 600 µL of 1 N sodium hydroxide for 20 minutes. After ten minutes, chloroform (500 µL) was added to elute the product from the diatomaceous earth into a well of a microtitre plate. After an additional 15 minutes, the process was repeated with additional chloroform (500 µL). The solvent was then removed by vacuum centrifugation.

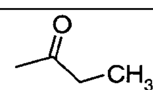
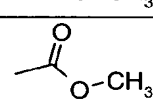
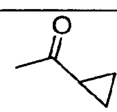
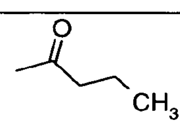
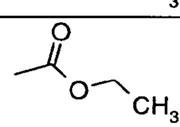
Part D

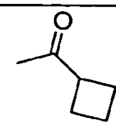
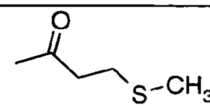
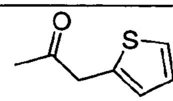
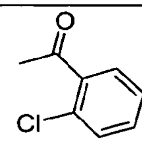
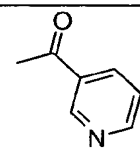
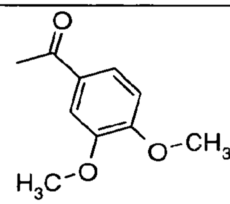
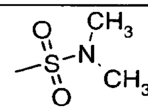
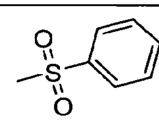
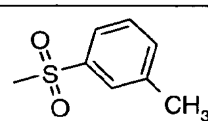
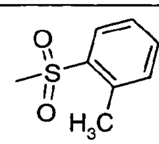
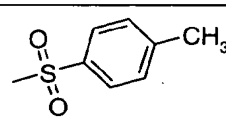
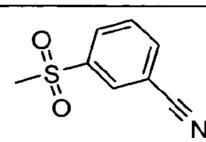
THF (1 mL) was added to each product from Part C located in a well of the microtitre plate described in Part C. The wells were capped and shaken until the mixture became homogeneous. The solutions were cooled to -20 °C, and tetrabutylammonium fluoride (300 µL of a 1.0 M solution in THF) was added. The plate was shaken, returned to the cold bath, and then allowed to warm to ambient temperature overnight.

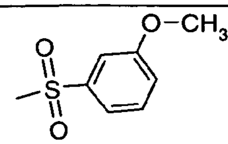
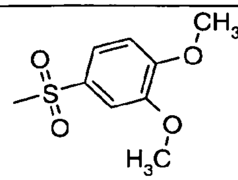
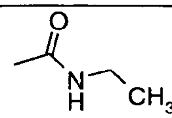
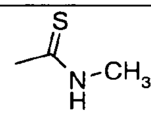
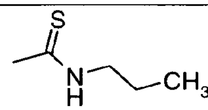
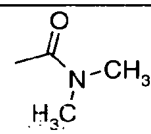
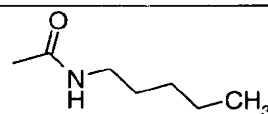
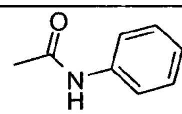
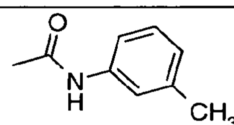
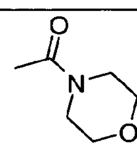
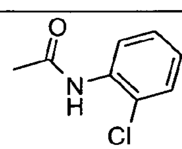
Trifluoroacetic acid (25 µL) was added to each well, and the plate was shaken carefully. The volatiles were then removed by vacuum centrifugation. Some of the compounds were purified by prep HPLC using the method described above. Other compounds were purified using a Waters Oasis Sample Extractions Cartridge MCX (5 cc) according to the following procedure prior to purification by prep HPLC. The sample was dissolved in methanol (2 mL) and passed through the cartridge. The cartridge was washed with methanol (2 x 2 mL) and transferred to a clean test tube. A solution of 7 N ammonia in methanol (3 x 2 mL) was then passed through the cartridge, and the basic solution was collected and concentrated. The table below shows the acid chloride, sulfonyl chloride, isocyanate, carbamoyl chloride, or sulfamoyl chloride used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

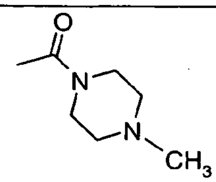
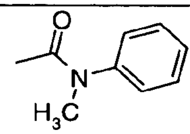
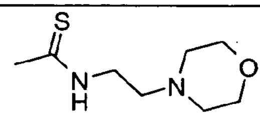
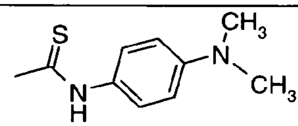
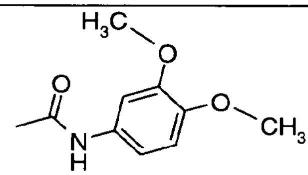
Examples 330-362



Example	Reagent	R	Measured Mass (M+H)
330	Propionyl chloride		326.1619
331	Methyl chloroformate		328.1409
332	Cyclopropanecarbonyl chloride		338.1617
333	Butyryl chloride		340.1750
334	Ethyl chloroformate		342.1549

335	Cyclobutanecarbonyl chloride		352.1789
336	3-Methylthiopropionyl chloride		372.1496
337	2-Thiopheneacetyl chloride		394.1355
338	2-Chlorobenzoyl chloride		408.1212
339	Nicotinoyl chloride hydrochloride		375.1569
340	3,4-Dimethoxybenzoyl chloride		434.1830
341	Dimethylsulfamoyl chloride		377.1381
342	Benzenesulfonyl chloride		410.1275
343	3-Methylbenzenesulfonyl chloride		424.1437
344	*o*-Toluenesulfonyl chloride		424.1450
345	*p*-Toluenesulfonyl chloride		424.1442
346	3-Cyanobenzenesulfonyl chloride		435.1243

347	3-Methoxybenzenesulfonyl chloride		440.1366
348	3,4-Dimethoxybenzenesulfonyl chloride		470.1510
349	Ethyl isocyanate		341.1724
350	Methyl isothiocyanate		343.1343
351	*n*-Propyl isothiocyanate		371.1641
352	*N,N*-Dimethylcarbamoyl chloride		341.1729
353	Pentyl isocyanate		383.2206
354	Phenyl isocyanate		389.1733
355	*m*-Tolyl isocyanate		403.1882
356	4-Morpholinecarbonyl chloride		383.1808
357	2-Chlorophenyl isocyanate		423.1343

358	4-Methyl-1-piperazinecarbonyl chloride		396.2111
359	*N*-Methyl-*N*-phenylcarbamoyl chloride		403.1892
360	2-Morpholinoethyl isothiocyanate		442.2038
361	4-(Dimethylamino)phenyl isothiocyanate		448.1911
362	3,4-Dimethoxyphenyl isocyanate		449.1924

CYTOKINE INDUCTION IN HUMAN CELLS

Compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α when tested using the method described below.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", Journal of Leukocyte Biology, 58, 365-372 (September, 1995).

<u>Blood Cell Preparation for Culture</u>

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole

blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

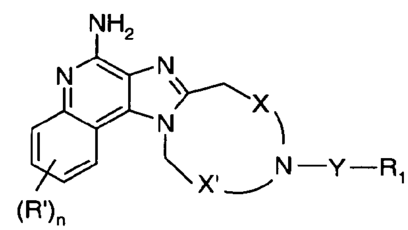
Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

What we claim is:

1. A compound of the Formula I:



I

wherein:

X is a bond or a straight chain or branched C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy wherein the hydroxy is bonded to a carbon atom other than a carbon atom adjacent a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted

or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the provision that when Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

each R_6 is independently selected from the group consisting of =O and =S;

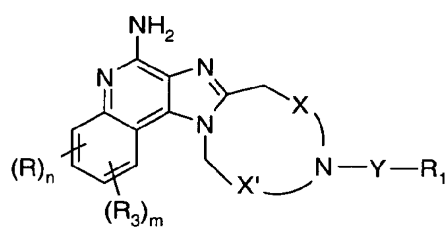
each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R' is a non-interfering substituent; and

n is 0 to 4;

or a pharmaceutically acceptable salt thereof.

2. A compound of the Formula II:



II

wherein:

X is a bond or a straight chain or branched C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy wherein the hydroxy is bonded to a carbon atom other than a carbon atom adjacent a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the proviso that when Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X''-R_4$,

$-Z-X''-Y'-R_4$,

$-Z-X''-Y'-X''-Y'-R_4$, and

-Z-X"-R_5;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

n is 0 to 4;

each X" is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

each Y' is independently selected from the group consisting of:

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

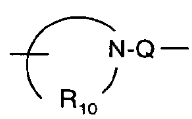
-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,



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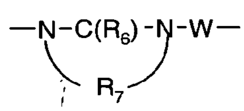

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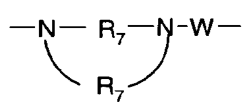

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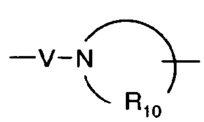

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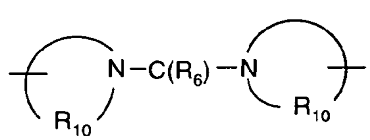

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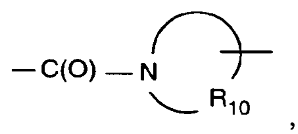
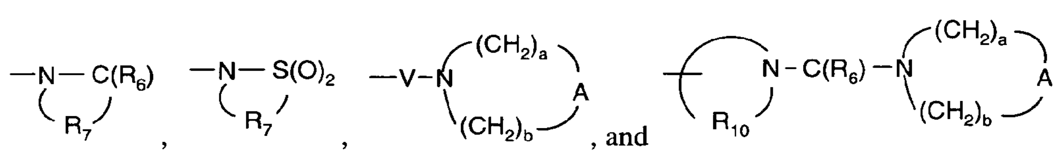


Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)$;

each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

3. A compound or salt of claim 1 wherein Y is $-S(O)_2-$ and R_1 is methyl.

4. A compound or salt of claim 2 wherein Y is $-S(O)_2-$ and R_1 is methyl.

5. A compound or salt of claim 1 wherein X is a bond and X' contributes one ring carbon atom.

6. A compound or salt of claim 2 wherein X is a bond and X' contributes one ring carbon atom.

7. A compound or salt of claim 1 wherein X is a bond and X' contributes two ring carbon atoms.

8. A compound or salt of claim 2 wherein X is a bond and X' contributes two ring carbon atoms.

9. A compound or salt of claim 1 wherein n is 0.

10. A compound or salt of claim 2 wherein n is 0.

11. A compound or salt of claim 2 wherein m and n are 0.

12. A compound or salt of claim 1 wherein the compound or salt induces the biosynthesis of one or more cytokines.

13. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 1 in combination with a pharmaceutically acceptable carrier.

14. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 2 in combination with a pharmaceutically acceptable carrier.

15. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 3 in combination with a pharmaceutically acceptable carrier.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 4 in combination with a pharmaceutically acceptable carrier.

17. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 1 to the animal.

18. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 2 to the animal.

19. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 3 to the animal.

20. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 4 to the animal.

21. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 1 to the animal.

22. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 2 to the animal.

23. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 3 to the animal.

24. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 4 to the animal.

25. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 1 to the animal.

26. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound of or salt claim 2 to the animal.

27. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound of or salt claim 3 to the animal.

28. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 4 to the animal.

PIPERAZINE, [1,4]DIAZEPANE, [1,4]DIAZOCANE, AND [1,5]DIAZOCANE FUSED IMIDAZOQUINOLINE AMINES

ABSTRACT OF THE DISCLOSURE

Piperazine, [1,4]diazepane, [1,4]diazocane, and [1,5]diazocane fused imidazoquinoline amines compounds, pharmaceutical compositions containing the compounds, intermediates, and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.